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Review Article

Clinically Significant Drug Interaction Profiles of Chloroquine Analogues with Adverse Consequences and Risk Management

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Abstract

The popularity of chloroquine (CQ) analogues, for malaria treatment in many countries emanates from it being cheap, widely available, relatively well tolerated, and having a rapid onset of action. Thus, CQ analogues are commonly sold as over-the-counter (OTC) medications. CQ analogues like hydroxychloroquine (HCQ) alone and/or other drugs in combination have been used as anti-inflammatory and immunomodulatory drugs in the treatment of various rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), sarcoidosis, dermatomyositis, Sjögren's syndrome, chronic juvenile arthritis, psoriatic arthritis, and have shown clinical benefits with an acceptable safety profile. As anti-inflammatory mechanism, CQ inhibits pro-inflammatory cytokine release, antigen processing and blocking the actions of histamine and phospholipase A_2. CQ analogue has also been studied for its potential as an enhancing agent in cancer therapies in various clinical trials. In many cases, the lysosomotrophic property of CQ appears to be important for the increase in efficacy and specificity to inhibit inflammatory disorders. Moreover, it is indicated that the efficacy of conventional therapies can be dramatically enhanced if CQ analogues are given in combination. Although majority of CQ analogue in combination therapies improves overall the outcome, such treatments are often associated with serious toxicities leading to fatal.

Keywords: Chloroquine analogues; Drug interaction; Safety profile; Toxicity.

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1. Introduction

The term 'Polypharmacy' describes the situation when a patient is prescribed for multiple medications. It often happens because many patients, especially elderly patients, may be under the care of multiple physicians: a patient who visits three different physicians may get three different prescriptions. These prescriptions may be committed to interact with

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each other, causing adverse drug reactions (sometimes dangerous ones) or reduced efficacy. Polypharmacy is not a trouble in itself, but all too often there is a lack of coordination among care providers resulting in a risk for drug–drug interactions (DDIs) [1,2]. Drug interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agents. Thus, drug interactions reflect a shift in drug activity or effect in the body as a result of another chemical's presence or activity. Drug interactions are usually considered either pharmacodynamics or pharmacokinetic. Adverse effects occur due to altered body burden of a drug as a result of a co-administered drug because the ability of one drug can alter the absorption, distribution, metabolism, and excretion (ADME) of the co-administered drug. Of the ADME properties, drug metabolism represents the most important and prevalent mechanism for pharmacokinetic interactions [3]. An understanding of drug interactions has become essential to the practice of medicine. The increasing pharmacopoeia, coupled with prolonged human life spans, makes polypharmacy commonplace. Drug interactions can be beneficial or detrimental. For example administration of drug product like carbidopa/levodopa combination would be beneficial. Levodopa is converted to dopamine in the central nervous system (CNS), thereby exerting an effect against symptoms of Parkinson's disease. Carbidopa acts as a chemical decoy, which binds to the enzyme that converts levodopa to domapine outside the CNS. This increases dopamine levels in the CNS while limiting side effects of increased dopamine in peripheral tissues. In combination, the paired drugs produce additive effects [4]. The outcome of drug combination can be harmful if the interaction causes an increase in the toxicity of the drug. For example, there is a considerable increase in risk of severe muscle damage if patients taking statins start taking azole antifungals (atorvastatin and fluconazole) [5]. Evaluation of drug–drug interaction potential is an essential factor for drug development and design. Screening for drug-drug interaction in early phases of drug development allows the avoidance of the development of drug candidates with high potential for adverse drug interactions and cost. Therefore, estimation of drug-drug interaction potential is a regulatory requirement that is required for new drug applications (NDA) to USA FDA [6,7]. Thus, drug interactions have become an important preventable iatrogenic complication.

Initially, antimalarial drugs, chloroquine (CQ) and its structural analogues were used primarily to treat malaria; however, they can be beneficial in combination with other drugs for many dermatological, immunlogical, rheumatological and bone diseases for which they are mostly used today. CQ and hydroxychloroquine (HCQ), two of the most fascinating drugs developed in the last 50 years, have been increasingly recognized in a myriad of other diseases in addition to malaria. In recent years, CQ and HCQ alone and/or in combination with other drugs are shown to have various immunomodulatory and immunosuppressive effects, and currently have an established role in the management of rheumatic diseases, lupus erythematosus, skin diseases, and in the treatment of cancer. Lately, additional metabolic, cardiovascular, antithrombotic, and antineoplastic effects of CQ and its analog are also known [8]. In this review, drug interaction is illustrated with

mostly used CQ analogues and the current evidence for their beneficial effects in various combinations and potential toxicities.

2. CQ analogues exhibiting the interaction

Relevant electronic literature is identified by performing PubMed and Google search covering the period from January 1988 to March 2013, using the search terms CQ analogues and drug interaction and pharmacokinetics and additional filters (species: humans; languages: English). Inclusion criteria included studies describing CQ analogue DDI with potential adverse consequences or inconsistent conclusions on clinical relevance. Exclusion criteria included studies that described CQ analogue DDIs with therapeutic benefits or insignificant clinical relevance. For practical purposes, the drug interactions of chloroquine analogues can be summarized in several ways (Table 1).

2.1. *Paracetamol*

CQ administration shortens the time (t_{max}) to reach peak plasma paracetamol concentration and increases significantly peak plasma paracetamol concentration (C_{max}). However, there is no effect of CQ on paracetamol metabolism [9,10]. The other report investigates the effect of aspirin, paracetamol and analgin on the kinetic profile of a single oral dose of CQ. Aspirin do not alter the kinetic parameters of CQ whereas paracetamol and analgin significantly enhance the C_{max} and area under the curve (AUC) of CQ [11].

2.2. *Antacids*

The absorption of CQ is moderately reduced by magnesium trisilicate, kaolin, and calcium carbonate. When CQ is given with either alone or separate doses of magnesium trisilicate or kaolin, magnesium trisilicate reduces the CQ area under the plasma concentration-time curve (AUC) by about 18.2% and the kaolin reduces it by about 28.6%. The absorption of CQ is decreased by magnesium trisilicate 31%, kaolin 47%, and calcium carbonate 52% [12]. Therefore, it is suggested to avoid loss of drug, that the CQ analogues should not be taken with these type gastrointestinal medications or that their administration should be separated by at least 4 h to reduce the risk of them interacting in the gut, thus preventing drug adsorption to the antacids/adsorbents, and loss of systemic availability. On mechanism, these antacids adsorb CQ thereby reducing the amount available for absorption by the gut [13]. The concomitant administration of CQ and antacid formulations containing any of these should be strongly discouraged [14,15].

2.3. *H_2-receptor antagonists*

Cimetidine reduces the metabolism and clearance of CQ. There is a 47.04% reduction in the AUC of monodesethyl-CQ, the major metabolite of CQ, in the test group when

compared with the control group because cimetidine inhibits the metabolism of CQ by the liver [16]. Ranitidine therapy is associated with no significant alterations in CQ oral clearance rate, elimination rate constant and apparent volume of distribution. Unlike cimetidine, ranitidine does not interact pharmacokinetically with CQ. Ranitidine, therefore, may be the H_2-receptor antagonist of choice for ulcer patients receiving CQ [17]. HCQ is predicted to interact with cimetidine in the same way as CQ. On the basis of these data for CQ and cimetidine, the manufacturer of HCQ states that cimetidine might inhibit HCQ metabolism.

Table 1. CQ analogues–drug interactions with risk of ventricular arrhythmias, particularly torsades de pointes.

Drug category	Examples	CQ analogues	Mechanism
Antiarrhymics	Amiodarone	CQ, HCQ, MQ, Q	Additive effect; causes prolongation of the QT interval.
	Aisopyramide	CQ, HCQ, MQ, Q	Additive effect; prolongs the QT interval.
	Procainamide	CQ, HCQ, MQ, Q	Additive effect; prolongs the QT interval.
	Sotalol	CQ, HCQ, MQ, Q	Additive effect; prolongs the QT interval.
	Propafenone	CQ, HCQ, MQ, Q	Additive effect; prolongs the QT interval.
	Quinidine	CQ, HCQ, MQ, Q	Additive effect; prolongs the QT interval.
Cardiac Glycosides	Digoxin	CQ, HCQ	CQ increases plasma concentration of digoxin
Antipsychotics	Phenothiazin, pimozide, chlorpromazine, haloperidol, pimozide, thioridazine	CQ, HCQ, MQ, Q	Additive effect; cause prolongation of the QT interval.
SNRI	Venlafaxine	CQ, HCQ, MQ, Q	Additive effect; these drugs cause prolongation of the QT interval
Antiepileptics		CQ, HCQ, MQ	These drugs lower seizure threshold
CNS Stimulants	Atomoxetine	CQ, HCQ, MQ	Additive effect; these drugs cause prolongation of the QT interval
Anticancer drugs	Porfimer	HCQ	Attributed to additive effects Increase risk of photosensitivity reactions
Anti-infectives	Ciclosporin	HCQ	Increase plasma concentrations of ciclosporin

Abbreviations: SNRI: serotonin norepinephrine reuptake inhibitors, HCQ: hydroxychloroquine, MQ: mefloquine, Q: quinine.

2.4. *Foods*

Patients often wish to take CQ with food to alleviate gastrointestinal irritation. Dosage with food may be beneficial as it appears to improve the absorption of CQ [18,19]. However, CQ interacts with micronutrients such as multivalent cations (iron, calcium, zinc, etc.) that cause reduction the absorption of the cations [18].

2.5. *Antidiabetics*

When HCQ is given in combination with insulin for 6 months, the glycated hemoglobin decreases significantly compared to placebo, and the daily insulin dose in patients treated with the combined insulin and HCQ therapy reduces at an average of 30%. Type 1 diabetic patients receiving insulin, HCQ has shown a dramatic return of sensitivity to insulin and a series of severe hypoglycaemic attacks heralds after 2 months of concurrent use, and it is necessary to drastically reduce the daily dose of insulin [8,20]. The patients with type 2 diabetes mellitus show a significant improvement in their glucose tolerance. The response seems to reflect decreased degradation of insulin rather than increased pancreatic output. These observations suggested that treatment with CQ or suitable analogues may be a new approach to the management of diabetes [20]. A case report suggests that HCQ reduces insulin dose with good glycaemic control in patients with rheumatoid arthritis [21,22]. Type 2 diabetic patients taking sulfonylurea drugs such as glibenclamide with HCQ have a significant improvement in their plasma glucose levels [23]. The anti-diabetic mechanism of CQ is a decrease in the insulin clearance and degradation rate and an increase in the secretion of C-peptide [8]. Patients with poorly controlled type 2 diabetes taking glibenclamide and HCQ, HCQ improves glycemic control more than placebo [8]. Although Zannah group suggested that HCQ in combination with the antidiabetic, biguanide drug metformin reduces blood glucose and lipid profile levels significantly in rats, clinically there are no interactions between HCQ and metformin [24,25]. Another interesting story based on their autophagy inhibiting property, recent several clinical studies suggest that CQ enhances the metformin-induced cell apoptosis and intensify the metformin-induced inhibition of cell proliferation of breast- and other cancers [26-28]. Reduced glucose levels or hypoglycaemia have also been reported with mefloquine and quinine [8,29]. Hypoglycaemia is a complication of falciparum malaria, which occurs mainly in severe life-threatening disease particularly in patients who are given quinine [8]. On mechanism, quinine reduces plasma glucose by stimulating the release of large amounts of insulin from the pancreas, whereas this is not shown for CQ, mefloquine, amodiaquine and halofantrine [8].

2.6. *Methotrexate*

In rheumatoid arthritis (RA), HCQ is usually a component of medication combinations, including triple-drug therapy with anticancer drug, methotrexate and sulfasalazine, a regimen that has been advocated as a safe, well-tolerated alternative to more expensive biologic therapies [30]. HCQ causes a minor increase in the area-under the time curve (AUC) of methotrexate. Methotrexate does not appear to alter HCQ pharmacokinetics. However, a single-dose CQ causes a moderate decrease in the maximum plasma levels of methotrexate by 20% and it's AUC by 28% in patients with RA, which in turn proved that that CQ has no significant effect on the pharmacokinetics of methotrexate, when compared in patients with juvenile arthritis taking methotrexate alone [3,8].

2.7. *Penicillamine*

A pharmacokinetic study reveals that patients with RA taking penicillamine together with CQ causes an increase peak plasma levels of penicillamine by about 55%. It is therefore concluded that the increased toxicity is associated with a reflection of increased plasma penicillamine levels which is dependent on CQ concentration [32].

2.8. *Antihistamines*

Chlorpheniramine (CP) appears to increase the levels and therapeutic efficacy of CQ. The addition of CP significantly increases the area under the AUC and peak concentration of CQ with acute uncomplicated falciparum malaria. Treatment with CQ-CP combination results in a shorter parasite clearance time and a higher cure rate (87.5%) compared to treatment with CQ alone (66.7%) [33]. In addition, CQ-CP combination also significantly increases the peak level of CQ in erythrocytes and half-life, when compared with CQ alone. As CP clearly enhances disposition of CQ, CQ-CP combination might be useful in the management of CQ-resistant infections [34]. In contrast to CP, promethazine (PR) has no statistically significant effect on the disposition of CQ. PR appears to increase the levels of intramuscular CQ and its metabolites, although no increase is seen with oral CQ. This is due to the fact that PR enhances the absorption of CQ from injection site or displaces it and its active metabolites from binding sites in the blood [35]. However, PR has no statistically significant effect on the plasma or erythrocyte bioavailability of CQ [34]. Thus, the concurrent use of CQ and CP, or PR, may result in a significant increase in CQ levels. This appears to improve the efficacy of CQ in malaria treatment without increasing serious adverse effects, particularly cardiac toxicity.

2.9. *Diazepam*

Since there is no effective treatment for severe CQ poisoning, the use of early mechanical ventilation, together with adrenaline and high doses of diazepam (both intravenously), to counteract cardiotoxicity gives encouraging results [36]. Thus, diazepam is used to treat the cardiotoxicity of CQ poisoning. Moreover, depending on the dose, diazepam possesses both antiarrhythmic and pro-arrhythmic properties [37]. Similarly, the overdosage with HCQ has managed in the same fashion of CQ overdosage [38].

2.10. *Thyroid hormone*

When stable hypothyroidism patients are treated with levothyroxine and given CQ and proguanil for antimalarial prophylaxis, an interaction between levothyroxine and the combination of CQ and proguanil reduces the control of hypothyroidism. This interaction may be more relevant to CQ, where it is used for long term treatment [39].

2.11. *Vasopressin*

CQ administration increases plasma vasopressin concentration and urinary sodium excretion because CQ has been shown to stimulate nitric oxide production [40].

2.12. *Combined hormonal contraceptives*

There is no clinically significant interaction between oral combined hormonal contraceptives (ethinylestradiol 30 μg with norethisterone 1 mg, or ethinylestradiol 30 μg with levonorgestrel 150 μg) and CQ, primaquine or quinine, or between oral hormonal contraceptives and mefloquine [41-43]. The use of CQ does not alter the inhibition of ovulation caused by the contraceptive, as assessed by mid-luteal progesterone levels and the lack of breakthrough spotting and bleeding [41,44].

2.13. *Gossypol*

Gossypol is a male antifertility agent with 99.9% efficacy. It is also known to have antibacterial, antiviral and antitumor activity [45,46]. The major problem associated with gossypol is to cause potassium depletion. However, the administration of gossypol and CQ together does not adversely affect serum electrolytes such as potassium, phosphate and sodium [47].

2.14. *Praziquantel*

Praziquantel (PZQ) is used to treat systemic worm infections such as schistosomiasis. The effect of CQ on the pharmacokinetics of PZQ indicates that CQ reduces the bioavailability and serum concentrations of PZQ to a significant extent. After taking CQ, the PZQ serum levels decrease by about 50% and do not reach the threshold level which is required to effectively kill schistosomes, compared with the control. An increased dosage of PZQ should be considered if CQ is given particularly to anyone who does not respond to initial treatment with PZQ [48].

2.15. *Agalsidase α/β*

α-Galactosidase A is an endogenous enzyme that hydrolyses terminal a-D-galactose residues in oligosaccharides and galactolipids into more easily digestible mono- and disaccharides. Agalsidase α and β are recombinant forms of α galactosidase A used for the long-term enzyme replacement therapy of Fabry disease (Anderson-Fabry disease) which is a rare X-linked recessive lysosomal storage disorder [49]. Fabry disease is characterized by a deficiency of the enzyme α-galactosidase A resulting in the intracellular accumulation of globotriaosylceramide (Gb) and other glycosphingolipids,

especially in vascular endothelium and smooth muscle. Agalsidase α/β should not be used with CQ which has the potential to inhibit intracellular α-galactosidase activity.

2.16. *Laronidase*

Laronidase is recombinant human α-L-iduronidase and is used as enzyme replacement therapy for the treatment of the non-neurological manifestations of mucopolysaccharidosis I [50]. Laronidase should not be given with CQ because of the potential risk of interference with the intracellular uptake of the enzyme.

2.17. *Vaccines*

The concomitant administration of CQ analogues, such as mefloquine, oral polio vaccine, or *oral* typhoid vaccine (Ty21a vaccine strain) on the immune response elicited by the *Vibrio cholerae* CVD103-HgR and *Salmonella typhi* Ty21a live oral vaccines have been investigated and the results suggest that cholera and typhoid vaccines do not affect each other. However, CQ significantly reduces the vibriocidal antibody response to oral cholera vaccine of *Vibrio cholerae* CVD103-HgR live oral vaccine whereas CQ can be given at the same time as *oral* typhoid vaccine without reducing its efficacy [51]. Similarly, the use of CQ with pyrimethamine and sulfadoxine do not affect the immune response to oral typhoid vaccine [52]. CQ significantly reduces intradermal human diploid-cell rabies vaccine [53] and CQ prophylaxis is associated with poor antibody response to this vaccine [54]. When vaccination against rabies with this vaccine is to be used, it is recommended that the vaccine should be given before starting CQ to avoid reducing the effectiveness of the vaccine. For yellow fever vaccine, CQ inhibits yellow fever virus *in vitro*, but the clinical evidence suggests that CQ do not affect antibody response to yellow fever 17D vaccines by concomitant oral administration of CQ [55]. It is also suggested that HCQ may also reduce the antibody response to primary immunization with intradermal human diploid rabies vaccine. Another study also indicates that CQ does not adversely affect the antibody response to yellow fever vaccine [56]. CQ does not alter the antibody response to tetanus, diphtheria, measles, oral poliomyelitis, oral typhoid (live), or BCG vaccines [52,57]. Thus, WHO recommends that people currently taking malaria prophylaxis or those unable to complete the 3-dose rabies pre-exposure regime before starting malaria prophylaxis with CQ analogues should receive pre-exposure rabies vaccination [58].

2.18. *Antibiotics*

2.18.1. Rifampicin

Discoid lupus patients treated by HCQ are given rifampicin, isoniazid and pyrazinamide for tuberculosis. The discoid lupus flares-up again but it rapidly responds when the HCQ dose is doubled [59]. The reason for this reaction is suggested that the rifampicin

increases the metabolism and clearance of HCQ so that it is no longer effective [60]. Neither isoniazid nor pyrazinamide is likely to have been responsible for the relapse [61].

2.18.2. *Ampicillin*

CQ reduces the absorption of ampicillin, but unaffected the absorption of ampicillin from bacampicillin (an ampicillin pro-drug). Clinically, CQ decreases the absorption of a single dose of oral ampicillin by about one-third [62]. The reason for the reduction in absorption is that the CQ irritates the gut so that the ampicillin is moved through more quickly, thereby reducing the time for absorption [63,64].

2.18.3. *Cyclosporine*

CQ analogues increase plasma concentrations of cyclosporine when added for malaria prophylaxis or treated onset rheumatoid arthritis [65-67]. Quinine has also reduced concentrations of cyclosporin [68].

2.18.4. *Quinolones (Ciprofloxacin)*

The first quinolone, nalidixic acid, was isolated as a byproduct of the synthesis of CQ. It has been available for the treatment of urinary tract infections for many years. The introduction of fluorinated 4-quinolones, such as gatifloxacin, ciprofloxacin, and moxifloxacin, represents a particularly important therapeutic advance because these agents have broad antimicrobial activity and are effective after oral administration for the treatment of a wide variety of infectious diseases. CQ modestly reduces ciprofloxacin levels (18% by CQ) which are below the minimum inhibitory concentration for *Plasmodium falciparum* [69,70]. The reduction in ciprofloxacin bioavailability has implicated for the management of infections resistant to CQ [71].

2.18.5. *Metronidazole*

The interaction between metronidazole and CQ associated with acute dystonic reactions such as facial grimacing, coarse tremors, and an inability to maintain posture in patient is reported [72].

2.18.6. *Azithromycin*

The anti-malarial property of azithromycin (AZ) is well-documented *in vitro* and in animal experiments, as well as in treatment and prevention clinical trials of both *Plasmodium falciparum* and *Plasmodium vivax*. As a monotherapy, AZ does not meet clinical standards of efficacy for treatment of falciparum malaria. However, the combination of AZ and CQ (AZCQ) has been shown to have synergistic activity *in vitro*

and *in vivo* against CQ-resistant strains of *P. falciparum* [73,74]. There is no pharmacokinetic interaction between AZ and CQ or its active metabolite, desethylchloroquine in healthy adults, indicating their clinically significant anti-malarial combination agents [75]. Thus, the efficacy and safety of a fixed-dose AZCQ for the treatment of symptomatic, uncomplicated *P. falciparum* malaria in adults are recently demonstrated in two multicentre phase 3 clinical studies in Africa [76] and in phase 2 studies in India and Colombia [77,78].

2.19. *Anticancer drug*

Porfimer sodium is used as a photosensitizer in the photodynamic therapy of non-small cell lung cancer, oesophageal cancer, and superficial bladder cancer. Porfimer sodium accumulates in malignant tissue on injection. It is then activated by laser light to release oxygen radicals within malignant cells, producing cytotoxicity. CQ analogues, HCQ is shown to effectively sensitize cancer cells to radiation and chemotherapy, without enhancing normal cells vulnerability [8,79,80]. Use of porfimer sodium with other photosensitive drugs especially CQ analogues cause intensive photosensitivity. A combination of CQ with tamoxifen or alkylating agent, cyclophosphamide does not result in higher toxicity than treatment with tamoxifen or cyclophosphamide alone. As inhibitors of autophagy, CQ analogue, HCQ is used to increase tumor-cell killing in conventional cancer therapeutics. Since glycolytic tumors are characteristically more acidic than surrounding normal tissues [81], CQ analogue is preferentially accumulated in the tumor and elicits greater efficacy in the inhibition of autophagy in the tumor than normal tissues [8,82].

2.20. *Antiretroviral therapy*

CQ analogues are used in clinical trials as an antiretroviral in humans with HIV-1/AIDS who often develop tumours, particularly when survival rates have been prolonged by antiretroviral treatments. CQ is added to a conventional therapeutic protocol (surgery plus radiotherapy plus chemotherapy) for glioblastoma in HIV-1-seronegative adults [8,83]. It is concluded that the median survival is doubled in the CQ analogue group compared with controls. Combined treatment with HCQ, hydroxyurea, and didanosine in antiretroviral naïve HIV patients suggests a low viral load, reduced viral replication, and higher the $CD4^+$ helper T cell count [84].

2.21. *Other antimalarials*

CQ increases the incidence of mouth ulcers in patients taking proguanil by 50% when both drugs are given as antimalarial prophylaxis [85]. The activities of CQ analogue are also affected when it is given with other antimalarial drugs such as mefloquine, quinine. The combination quinine and CQ acts as an antagonist each other [86]. Mixtures of CQ

analogue with quinine, mefloquine, amodiaquine, artemisinin, or pyrimethamine-sulfadoxine are also antagonistic *in vitro* against *Plasmodium falciparum* [87].

2. 22. *Azathioprine*

HCQ in combination with azathioprine, an immunosuppressant drug, prompts a major recovery in a patient with sensory neuropathy syndrome [8].

2.23. *Digoxin*

HCQ increases plasma concentrations of cardiac glycoside drug, digoxin. An increase in the plasma-digoxin concentration by over 70% is noted in elderly patients given HCQ for rheumatoid arthritis in addition to long-term digoxin therapy [88].

2.24. *Antiarrhythmics (amiodarone)*

CQ analogue is generally considered as safe drug for cardiovascular system, especially when given at the correct dose and administered appropriately [89]. Although the concurrent use of CQ with antiarrhythmic drug, amiodarone may increase the risk of torsade de pointes, there are no published clinical cases of the interaction. There are reports only on heart wave transmission called QT prolongation, a marker of abnormal ventricular re-polarisation, in a patient taking CQ, but this is secondary to long term use for systemic lupus erythematosus [90]. CQ prolongs the electrocardographic QT interval and an increased risk of inducing life-threatening ventricular arrhythmia called torsades de pointes when CQ analogues are given with various drugs such as antimalarial drugs (mefloquine, halofantrine and quinine); tricyclic antidepressants (phenothiazine antipsychotic, pimozide); antiarrhythmics (disopyramide, flecainide, procainamide and quinidine); beta blocker (sotalol) and the antihistamines (astemizole and terfenadine). There is an increased risk of convulsions when CQ is given with mefloquine. Drugs that increase the risk of torsades de pointes listed in Table 1, and a frequently updated list can be found online at www.torsades.org.

2.25. *Antiepileptics*

Carbamazepine is the drug of choice for the management of trigeminal neuralgia [91-93]. Valproate is normally the drug of choice for myoclonic seizures, including those associated with juvenile myoclonic epilepsy [94,95]. CQ antagonizes the antiepileptic activity of carbamazepine and valproate by lowering the convulsive threshold. Low serum concentrations of valproate have been observed in patients taking mefloquine and lowered the convulsive threshold.

2.26. *Antipsychotics*

Pretreatment with CQ analogue can markedly increase the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, one of the major metabolites of chlorpromazine levels in schizophrenic patients [96]. The raised plasma concentrations appeared to be associated with a greater level of sedation when given CQ analogue.

2.27. *Antihypertensive β blockers*

HCQ increases the blood levels of metoprolol and other similarly metabolized β blockers. HCQ increases the AUC and peak plasma levels of metoprolol by 65% and 72%, respectively [97]. Here, HCQ inhibits metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6. CQ interacts with metoprolol in the same way as HCQ [98].

2.28. *Amlodipine and imipramine*

Hypertensive patients, normally used to take antihypertensive Ca^{2+}-channel blocker, amlodipine 5 mg daily for 3 months with optimal blood pressure control. However, when he takes CQ analogue for the treatment of malaria, an acute hypotensive episode may occur due to combination of amlodipine with CQ [99]. No pharmacokinetic interaction is observed in 6 healthy subjects when treated with CQ and tricyclic antidepressant, imipramine [100].

2.29. *Methylene blue*

When methylthioninium chloride (methylene blue) is given to the patients taking CQ analogue, there is a decrease in the AUC of CQ (about 20%) in comparison with a control group received CQ with placebo [101].

2.30. *Deoxyribonucleic acid (DNA)*

Qualitative and quantitative experiments suggest that an interaction between CQ and DNA involves in electrostatic attraction between the protonated ring system of CQ and the anionic phosphate groups of DNA, and a more specific interaction apparently involving the aromatic ring portions of CQ and nucleotide bases. The secondary structure of DNA affects its binding to CQ and, conversely, complex formation protects the native helical configuration against thermal denaturation. These studies regarding the interactions of CQ with DNA provide information about the structural basis of binding phenomena of CQ in DNA molecules. These studies also indicate that CQ exists as a doubly protonated cations at physiological pH in dilute aqueous solutions and that it is this molecular form that binds to nucleic acids. Subsequently, the biological properties of DNA are markedly altered by its interaction with CQ, and that such complex formation

can inhibit enzymatic depolymerization of DNA and interfere with its function as a primer for the DNA-dependent DNA and RNA polymerase reactions [102]. The CQ analogues block DNA and RNA biosynthesis and produce rapid degradation of ribosomes and dissimilation of ribosomal RNA. By intercalation, CQ inhibits DNA and RNA polymerase reactions *in vitro* and DNA replication and RNA transcription in susceptible cells [103]. CQ interferes with protein synthesis *in vivo* and *in vitro* [8,104].

2.31. *UV light*

Ability of CQ analogues for light filtration is one of the mechanisms responsible for the effectiveness of CQ analogues in systemic lupus erythematosus (SLE) and other light-sensitive disorders. The topical application of CQ and mepacrine (quinacrine) decreases erythema produced by a high-pressure mercury lamp [105]. Oral administration of CQ decreases UV erythema and carcinogenesis on the ear [8,106]. Systemically administered CQ has been shown to protect animals against radiation damage and the carcinogenic effect of grenz rays [107,108]. The cutaneous reactions and delayed erythema to light in patients with SLE and polymorphous light eruption are blocked by intradermally injected HCQ, but not with topical application, suggesting an alternative mode of action other than as a sun-screen [109]. Thus, CQ analogues decrease UV-induced reactions both in light-sensitive and normal individuals, and that they down-regulate several photo-induced cutaneous disorders including SLE. However, the mechanism of action for this protective effect against UV does not seem to be related merely to absorption and screening, but rather to inhibition of the UV-induced inflammatory reaction [110].

3. Discussion

Simultaneous co-administration of multiple drugs to a patient is highly practical. A patient may be co-administered multiple drugs to allow effective treatment of a disease (e.g., cancer, HIV infection) or for the treatment of multiple disease or disease symptoms. It is now known that drug–drug interactions may have serious, sometimes fatal, consequences. Serious drug-drug interactions have led to the necessity of a drug manufacturer to withdraw or limit the use of marketed drugs which is a major cause of economic burden for pharmaceutical companies. A major mechanism of adverse drug–drug interactions is the inhibition of the metabolism of a drug by a co-administered drug, thereby elevating the systemic burden of the affected drug to a toxic level [111,112]. In general, CQ analogues are increasingly available over the counter (OTC) drug and on-line without prescription. CQ overdosage is the most severe and frequent cause of intoxication with other antimalarial drugs and CQ is often used for suicide attempts. Severe toxic manifestations may occur within 1- 3 h and fatal outcomes usually occur within 2- 3 h of drug ingestion. The major clinical symptoms are of neurological, respiratory, and cardiovascular toxicity [8,113]; death is usually due to cardiac arrest related to the direct effect of CQ on the myocardium [36]. Overdosage with HCQ has responded to measures

similar to those used in the management of CQ overdosage [38]. Ultimately, we may be able to develop very effective modalities by combining a certain class of CQ derivatives and inhibitors directing specific cellular targets from these studies (Table 2). This "customized" combinational approach will likely provide us a very powerful means to control many different diseases like cancers in future.

Table 2. Summary of drug interactions with CQ analogues.

Drug	Drug	CQ influence and/or potential risk	Recommendation
CQ	Paracetamol	↑plasma paracetamol conc. by shortening time (t_{max})	Avoid co-administration
CQ	Antacids	Absorption of CQ is moderately reduced by antacids	Separate doses by at least 4 h
CQ	Cimetidine	Reduction of metabolism and clearance of CQ	Consider ranitidine as an alternative or take cimetidine at least 2 h after CQ
CQ	Ranitidine	There is no interaction with CQ	
HCQ	Insulin	↑ insulin sensitivity in type 1 diabetic patients	Check blood sugar level and reduce daily dose of insulin
HCQ	GC	↓ insulin clearance and degradation rate in type 2 diabetic patients	Check blood sugar level and adjust daily dose of GC
CQ	Metformin	CQ enhances the metformin-induced cell apoptosis of cancer patients	
CQ	Penicillamine	CQ increases peak plasma levels of penicillamine	Monitor acute toxicity
CQ	CP	↑ plasma level and therapeutic efficacy of CQ	Monitor regularly cardiac toxicity
CQ	Ciprofloxacin	CQ modestly reduces ciprofloxacin levels	Avoid co-administration
CQ	Ciclosporin	↑plasma conc. of ciclosporin	Monitor renal function weekly
HCQ	Porfimer	↑risk of photosensitity reactions	Avoid exposure of skin and eyes to direct sunlight
CQ, HCQ	digoxin	↑plasma conc. of digoxin	Monitor digoxin levels; watch for digoxin toxicity
CQ	kaolin	↓ CQ levels absorption	Separate doses by at least 4 h
CQ	antiepileptics	CQ decreases seizure threshold	Care with co-administration; ↑dose of antiepileptic
CQ	antimalarials, MQ	Additive effect; risk of seizures	Warn patient of the risks
CQ	bupropion	↑risk of seizures especially elderly people	Extreme caution. dose adjustment carefully (≥ 450 mg/day).
PQ	Mepacrine	↑primaquine levels by inhibition of metabolism	Warn patients to report the early features of primaquine toxicity
CQ	Micronutrient	Multivalent cations will cause adsorption interaction	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)

Where, ↑ indicates increased and ↓ decreased; HCQ: hydroxychloroquine, MQ: mefloquine, PQ: primaquine, GC: glibenclamide and CP: chlorpheniramine

4. Conclusion

CQ analogues, especially HCQ were developed primarily for the treatment of malaria and now are credited for saving the lives of thousands of patients with various nonmalarial diseases. Since the first use of antimalarial agents nearly a century ago, their effects on diseases in nearly all major branches of medicine have been increasingly recognized, including the fields of immunology, oncology, hematology, dermatology, cardiology, and infectious diseases. Rheumatologists, dermatologists and other professionals recognized their effectiveness for various pathologies in their specialties, but although these drugs are FDA approved for malaria, lupus erythematosus (different forms) and rheumatoid arthritis are not recognized for many other conditions which are far more relevant today. The marketing and biopharmaceutical interests in these medications have disappeared due to their interaction with various drugs. For this reason, we gathered the necessary information for CQ analog-drug interactions and we offer to practice various professionals to use as they see the best fit, with the hope that these data will be of benefit in providing better care for the patients who need these drugs.

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