Original Article

Potential Drug-drug Interactions and Adverse Drug Reactions Associated with Hydroxychloroquine

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ABSTRACT

Introduction: COVID-19 is a pandemic disaster and a health emergency of prime focus for all the world economies. Various prophylactic treatments are considered to combat the disease. Hydroxychloroquine drug is one such option that is given much attention as an armor against SARS COV-2 pandemic. Evaluation and assessment of drug interactions and ADRs is required from ethical concern to justify the use of HCQ on such large scale. **Methods:** We have performed an analysis of HCQ drug interactions on Micromedex®. We have reviewed literature of HCQ pharmacokinetic properties, ADRs/ ADEs and toxicities associated with the use of HCQ drug on PubMed, Google Scholar and CDC database. **Results:** There are around 180 drug interactions possible with HCQ. Out of them 13 are of contraindicated severity level and other 165 are of major severity and 2 of them are moderately severe. Most of the interactions are coupled with QT prolonging agents (170), Cardiac arrhythmias is possible with the concomitant use of at least 2 drugs, 4 drugs leads to Torsade de points. System organ level ADRs are also evaluated along with various precautions, warnings and contraindications. **Conclusion:** Currently various options are available such as chloroquine, HCQ- azithromycin, remdesivir, plasma therapy and many others in the pipeline. Majority of patients are asymptomatic, therefore blind use of HCQ should be prohibited. Considering DDIs and ADRs associated with HCQ use, it should be used under clinical care with emphasizing proper screening in cardiovascular co-morbid patients.

Key words: Hydroxychloroquine, COVID-19, Drug Interactions, Adverse Drug Reactions, Micromedex®.

INTRODUCTION

Corona Virus Disease 2019 (COVID-19) has been declared as a pandemic by World Health Organization on 11 March 2020.[1] Originating from Wuhan (in China), the virus has affected every life on the planet, directly or indirectly. Till date, more than thirty million seven hundred eighteen thousand humans are infected with new corona virus out of which there are more than seventy-four million active cases globally with 956,876 deaths so far.[2] till today there is no regulatory approved antidote or curative treatment available against the disease in India, other than supportive therapy. Therefore, various prophylactic treatments are considered to combat the disease. Hydroxychloroquine (HCQ) drug is one such option that is given much attention as an armor against SARS COV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) pandemic.

HCQ was first discovered during WWII, approved in 1955 for its antimalarial action. Since then it has been approved for various autoimmune diseases such as Rheumatoid Arteritis (RA) and Systemic Lupus Erythematosus (SLE).[3] World Health Organization has placed HCQ in Essential Drug List.[4] The clinical data so far presented is not feasible enough to justify HCQ use in all of the races of human population, despite this fact, health authorities globally are bating on HCQ as game changer.[5,6] Therefore a careful analysis of literature to identify potential drug-drug interactions and adverse drug effects associated with the use of HCQ is ethically required for public safety.

Drug-Drug Interactions

Drug-Drug Interactions also termed as

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DDIs are considered as preventable medication-related problems. Drug-Drug Interactions occur when two or more drugs (especially active pharmaceutical ingredients) interact with each other leads to alteration in efficacy or toxicity of the drugs involved. Polypharmacy increases the chances of drug interactions as chances of DDIs are proportionate to the number of drugs prescribed per prescription order.[7,8]

Drug-Drug Interactions results in harmful outcomes to the patients either by increasing the drug toxicity or by reducing its therapeutic efficacy. An analysis of multiple studies in over 370,000 patients demonstrated that 2.2%–70.3% of patients are subjected to potential DDIs. An observation by Nolan and O'Malley demonstrated that the patients who took multiple medications (ten or more) were subjected to almost 90% probability of experiencing one or more clinically relevant DDIs which are often related with either prolonged hospitalizations or readmissions.[7,8]

The change in the pharmacological action or therapeutic response of any drug due to concomitant administration of another drug is termed as drug-drug interaction.[9] Majority of this type of interactions arises due to pharmacokinetics incompatibility of two or more drugs/molecules.

A drug-drug interaction (DDIs) leads to medication error.[10] On the basis of therapeutic response, DDIs could be categorized in to two types:

Synergistic DDIs: Drug synergy is an outcome of two or more interacting drugs which (due to similar) leads to combined boost of drug efficacy. Drug Synergy is a goal of combinational drug therapy but sometimes it has toxic effects too.[11] Synergistic drug interactions generally considered to be therapeutically effective in combination drug therapies.[12]

Antagonistic DDIs: Drug antagonism is an outcome of two or more interacting drugs which (due to opposite action) leads to an undesirable, reduced therapeutic efficacy.[13]

Adverse Drug Reaction

An Adverse Drug Reaction commonly abbreviated as ADR, is an undesirable, unwanted response of a drug. ADRs affects not only treatment efficacy but also patient's quality of life, as they may enhance morbidity and sometimes results in mortality, as a result of which patients loses confidence in or have negative emotions toward Health care professionals (HCPs). There are many contributing factors associated with the ADRs such as increase in the number of drugs (polypharmacy), geriatric group, idiosyncrasy, Drug Interactions and high dosesetc.[14]

Clinical Database

Drug Information resources are the databases consist of critically examined and relevant (current) data about drugs and their utilization information both clinical and scientific. The efficient use of drug information is an important skill for all healthcare providers. There has been an explosion of information available on the Internet for both the health care professional and the consumer. Micromedex® is one such source of clinical relevant drug information which is trusted globally.[15,16] Some of the drug information sources are represented in Table 1.

Micromedex®

Micromedex® is an online database which includes referenced evidence-based information about drugs. Micromedex® is a tertiary resource designed to provide information to the health care professional about clinical inquires. This resource, commonly used in the hospital or academic setting, provides a variety of information in the areas of drug information, poison information, acute care

Table 1: Globally used clinical drug databases.

S. No	Drug Information Resources	Access	Developer	Country of Origin
1.	DrugDex® System	Paid Subscription	Thomson Reuters MICROMEDEX®2.0	United States of America
2.	Martindale		Pharmaceutical Press	United Kingdom
3.	Lexi-Drugs®		Lexi-Comp, Inc.	United States of America
4.	Drug Facts and Comparisons®	Free	Wolters Kluwer Health—Facts and ComparisonsTM	United States of America
5.	Epocrates®Online		Epocrates, Inc. www.epocrates.com	United States of America
6.	A-Z Drug Facts™		Wolters KluwerTM Health www.drugs.com	United States of America

Various paid and free clinical databases used across the globe for clinical information retrieval

medicine and patient education. Information is provided as full-text and is referenced throughout. Although Micromedex® is a large database, the primary literature is readily referenced and easy to access. Therapeutic indications are given a graded evidence rating with usage recommendations. For the clinician, Micromedex® offers comprehensive, easy-to-read, extensively referenced data on drugs.[15,16]

MATERIALS AND METHODS

We have utilized Micromedex® drug interaction tool to perform an Analysis of HCQ drug interactions on Micromedex® software. Drug Interactions associated with HCQ were searched and filtered on the basis of documented evidences. The possible outcome of such drug interactions were also analyzed. The potentiate agents capable of producing significant drug interaction with HCQ, were further categorized according to severity level of possible outcome. The gathered evidences are further processed for statistical interpretation through MS Excel. We have also reviewed literature of HCQ pharmacokinetic properties, ADRs and toxicities associated with the use of HCQ drug on PubMed, Google Scholar and CDC database to represent possible toxicities with the use of this drug.

RESULTS

There are around 180 possible drug interactions possible with HCQ. Out of them 13 are contraindicated severity level and other 165 major severity and 2 of them are moderately severe (As represented in Figure 1).

Total 13 drug interactions are of contraindicated severity level and other 165 are of major severity and 2 of them are moderately severe

Micromedex® drug Interaction tool analysis to evaluate and identify HCQ related possible Drug-Drug interactions result is summarized in Table 2.

Contraindicated severity signify to the drugs which are contraindicated for concurrent (together) use, Major severity signify to the drug interactions which require clinical intervention to decrease or safeguard life-threatening adverse effects, whereas Moderate severity signifies to drug interactions which may require change in treatment as they may exacerbate patient's morbidity.

The documentation of these Drug interactions is good with 5 drugs and fair with rest 175 drugs. A Good documentation signifies that the interaction among drugs exists, but specific clinical studies are missing, whereas a Moderate suggests that the available documentation is not strong, but the pharmacologic data suggest that the interaction possibility is good for a pharmacologically similar drug.

Most of the interactions are coupled with QT prolonging agents (170) such as Ceritinib, Ivosidenib, Encorafenib and Efavirenz (Figure 2) which are potentiate to result in further cardiac abnormalities. Cardiac arrhythmias is possible with the concomitant use of at least 2 drugs i.e., Entrectiniband, Pitolisant. Aurothioglucose has contraindicated severity with major fair documentation of blood dyscarsias when used as concomitant drug along with HCQ. 4 drugs (Amisulpride, Donepezil, Amiodarone, Sotalol and Sulpiride) may leads to Torsade de points.

Most of the Hydroxychlorquine drug interactions are coupled with QT prolonging drugs (170). HCQ interaction with at least 2 drugs (Entrectiniband, Pitolisant) May leads to Cardiac arrhythmias and 4 drugs (Amisulpride, Donepezil, Amiodarone, Sotalol and Sulpiride) may cause Tor se de points.

Use of contraindicated drugs as concomitant therapy should not be done with HCQ to prevent further morbidity. Safer drug regimen should always be preferred under regular clinical monitoring. The complications with use of HCQ are mostly associated with cardiac functioning, therefore while selection of patients, ECG (Electrocardiogram) should be rule out prior to initiation of therapy. Patient with history of cardiovascular disorder must be evaluated and dose calculation as per the body weight could also be considered.

Torsade de pointes are characterized by increased risk of a polymorphic ventricular tachycardia whereas drug-induced QT prolongation syndrome is symbolized by an increased QT interval in an electrocardiogram (ECG). Although the cardiovascular risk associated with QT prolonging drugs is well established but treatment with such therapeutic agents is sometimes needed. Therefore the possible risks of such therapies should be evaluated against benefits outcomes before initiation. Polypharmacy, especially of multiple QT prolonging drugs should be avoided as much as possible. Underlying risk factors, Co-morbidities must be evaluated. If possible and available, alternative drugs could also be considered thoroughly.[17]

Discussion: HCQ is a relatively safe drug. Specific drug reactions like leukopenia, aplastic anemia, agranulocytosis, RBCs destruction (in patients with G-6-PD deficiency), thrombocytopenia and worsening of psoriasis could be prevented with proper screening of patients before

Table 2: HCQ Drug- drug Interactions with Severity Level (Micromedex®).

Drugs with contraindicated seviarity to HCQ					
Aurothioglucose	Mesoridazine	Thioridazine	Dronedarone	Terfenadine	Bepridil
Cisapride	Sparfloxacin	Saquinavir	Ziprasidone	Piperaquine	Pimozide
Amisulpride					
Drugs with major severity to HCQ					
Lofexidine	Mefloquine		Pipamperone		Tetrabenazine
Quinidine	Anagrelide		Galantamine		Sultopride
Disopyramide	Perphenazine		Mizolastine		Lumefantrine
Procainamide	Ciprofloxacin		Tolterodine		Arsenic trioxide
Erythromycin	Fluoxetine		Nelfinavir		Invosidenib
Methotrimeprazine	Ofloxacin		Ranolazine		Ribociclib
Metronidazole	Octreotide		Vardenafil		Encorafenib
Chloroquine	Mifepristone		Voriconazole		Donepezil
Probucol	Clomipramine		Gatifloxacin		Auranofin
Quinine	Protriptyline		Iloperidone		Certinib
Methadone	Goserelin		Moxifloxacin		Amiodrone
Promethazine	Nafarelin		Gemifloxacin		Entrecitinib
Desipramine	Moricizine		Hydroquinidine		Zuclopenthixol
Haloperidol	Halofantrine		Telithromycin		Efavirenz
Imipramine	Fluconazole		Escitalopram		Quetiapine
Prochlorperazine	Paroxetine		Solifenacin		Sertraline
Amitriptyline	Ondansetron		Sorafenib		Panobinostat
Doxepin	Azithromycin		Sunitinib		Sulpiride
Chlorpromazine	Foscarnet		Dasatinib		Sotalol
Tamoxifen	Apomorphine		Posaconazole		Aripiprazole lauroxil
Cyclobenzaprine	Clarithromycin		Vorinostat		Triclabendazole
Droperidol	Toremifene		Paliperidone		Osimertinib
Aripiprazole	Granisetron		Lapatinib		Glasdegib
Trimipramine	Tacrolimus		Nilotinib		Clofazimine
Trazodone	Itraconazole		Degarelix		Inotuzumab
Ketoconazole	Deslorelin		Asenapine		Ozogamicin
Pentamidine	Histrelin		Telavancin		Lefamulin
Domperidone	Felbamate		Pazopanib		Siponimod
Clozapine	Buserelin		Fingolimod		Buprenorphine
Gonadorelin	Venlafaxine		Eribulin		Hydroxyzine
Sodium phosphate	Risperidone		Vandetanib		Pitolisant
Sodium phosphate	Triptorelin		Rilpivirine		Pimavanserin
Monobasic	Formoterol		Telaprevir		Macimorelin
Sodium phosphate	Citalopram		Vemurafenib		Lenvatinib
Dibasic	Alfuzosin		Crizotinib		Vilanterol
Astemizole	Levofloxacin		Pasireotide		Dabrafenib
Flecainide	Fosphenytoin		Vinflunine		Delamanid
Norfloxacin	Sevoflurane		Bedaquiline		Ebastine
Propafenone	Zotepine		Ivabradine		Tizanidine
Famotidine	Dofetilide		Atazanavir		Sertindole
Ibutilide	Dolasetron		Leuprolide		Olanzapine
Ritonavir					
Drugs with moderate severity to HCQ					
Digoxin	Lanthanum carbonate selected anti malarials				

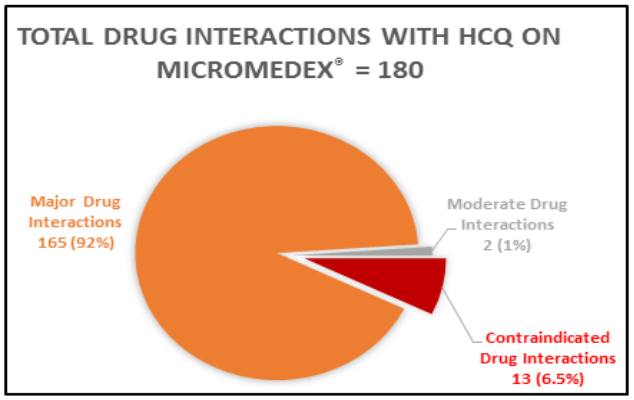

Figure 1: HCQ Drug- Drug Interactions Severity analysis chart (Micromedex®)

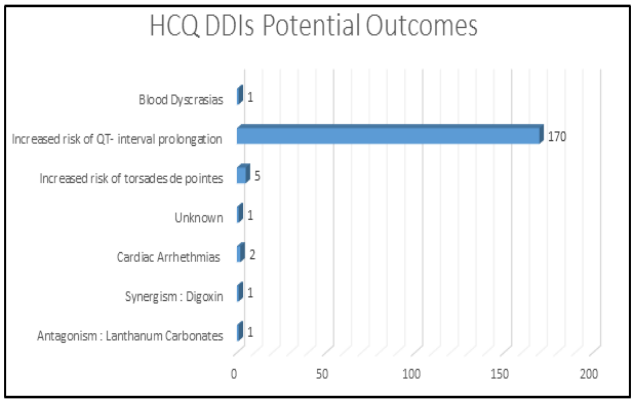

Figure 2: HCQ Drug-Drug Interactions Potential Outcome analysis.

initiation of therapy.

Some common ADRs associated with HCQ use are nausea, vomiting, headache, Abdominal cramping, diarrhea, anorexia, irritability, liver dis-functioning, nervousness, seizure, lassitude, psychosis, vertigo, nightmares, pigmentation changes, rash, pruritus and tinnitus are also well documented.

Complicated adverse drug effects of HCQ therapy are seen mainly in drug accumulation cases which lead to Cardiopathy and Retinopathy. Cardiac changes such as Arrhythmias, torsade de pointes, vasodilation, hypotension, suppressed myocardial function, QT interval prolongation, Cardiomyopathy, cardiac failure and eventual cardiac arrest may be present. In retinopathy patient may experience corneal changes (edema and opacities), Visual disturbances, photophobia color vision abnormalities decreased dark adaptation, halo around lights and blurred vision (Figure 3).[18]

Other than cardiac and ophthalmic complications hydroxychlorquine is known to affect other major body systems as well.

Summary Product Characteristics (SmPCs) of PLAQUENIL® tablet which contains Hydroxychloroquine as an Active Pharmaceutical Ingredient, highlights the warnings of possible health hazards associated with the use of HCQ along with uses with Precautions in certain co-morbidities and contraindicated patients. Table 3 represent the safety summary of HCQ SmPC.

There are various factors that affect the development of ADRs such as age, sex, drug dose, co-morbidity. Careful evaluation of these factors could prevent and reduce the incidence of unwanted and undesired ADRs. Counseling, health education and reconciliation of medications are essential duties which must be performed by HCPs as part

Table 3: Oral HCQ SmPC (summary product characteristics) safety summary.[17]

HCQ Safety Advisory	
Contraindication	Hypersensitivity to 4- Aminoquinolines
Precautions	Gastrointestinal disorders Neurological disorders Blood disorders sensitivity to quinine Hepatic/Renal Disease alcoholism or conjunction with hepatotoxic drugs
Warnings	Retinal irreversible damage Fatal Cardiac outcomes, like QT prolongation and Cardiomyopathy Exacerbation of psoriasis Neuropathy Hypoglycemia Hemolysis in G-6-PD

Contraindications, Precautions and Warnings associated with the use of Hydroxychloroquine as per SmPC submitted by Marketing Authorization Holder to US FDA.

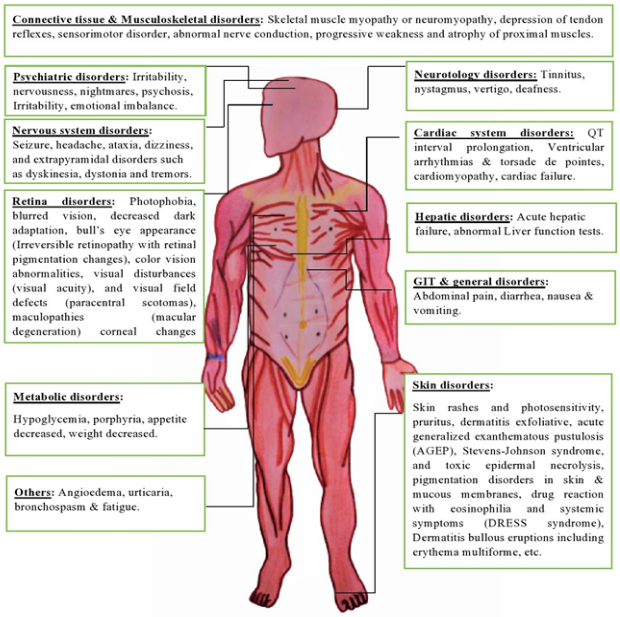

Figure 3: Various Adverse Drug Reactions associated with Hydroxychloroquine.[17]

of therapy plan to achieve desired therapeutic outcome. Drug Information resources and Internet should also be utilized in evidence based medication decision making process which would make aware HCPs about advancement in medical field and basics such as of drug-dosing, lethal drug interaction, possible adverse events. As such relevant clinical information is mandatorily required to prescribe medication for the optimum therapeutic outcome. The Benefits of medical therapy must always outweigh the risks associated with it.[19]

CONCLUSION

COVID-19 is a pandemic disaster and a health emergency of prime focus for all the world economies. Currently various options are available such as chloroquine, HCQ-azithromycin, dexamethasone, remdesivir, plasma therapy etc. and many others in the pipeline. Majority of patients are asymptomatic, therefore blind use of HCQ should be prohibited. Considering DDIs and ADRs associated with HCQ use, it should be used under clinical care with emphasizing proper screening in cardiovascular co-morbid patients.

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CONFLICT OF INTEREST

The authors declare as no conflict of interest of any kind with anybody

ABBREVIATIONS

ADE: Adverse Drug Event; **ADR:** Adverse Drug Reaction; **CDC:** Centre for Disease Control; **COVID19:** Corona Virus Disease 2019; **DDI:** Drug Drug Interaction; ECG: Electrocardiogram; **G-6-PD:** Glucose-6-Phosphate Dehydrogenase; **GIT:** GastroIntestinal Tract; **HCP:** Healthcare Provider; **HCQ:** Hydroxychloroquine; **RA:** Rheumatoid Arteritis; **SARS COV2:** Severe Acute Respiratory Syndrome Corona Virus 2; **SLE:** Systemic Lupus Erythematosus; **SmPC:** Summary Product Characteristics; **US FDA:** Unites States Food and Drug Administration; **WW II:** World War II.

SUMMARY

Adverse drug reactions and Drug Drug interactions associated with the use of Hydroxychloroquine in COVID-19 are potentially harmful in nature. Cardiac functioning of patients should be evaluated prior to initiation of therapy. Drug information resources should also be utilized for the assessment of possible drug interaction in case of co-morbidities and multiple drug therapy. Majority of ADRs are preventable in nature with proper dose adjustment. Continuous monitoring and regular follow up of patients, treated with HCQ is advised.

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