Original Article

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Pharmacology Section

Possible Drug-Drug Interactions of Hydroxychloroquine with Concomitant Medications in Prophylaxis and Treatment of COVID-19: Multiple Standard Software Based Assessment

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ABSTRACT

Introduction: It is a crucial time for the medical community to cope up with novel Coronavirus Disease 2019 (COVID-19). The empirical evidence for the effectiveness of Hydroxychloroquine (HCQ) in COVID-19 is currently very limited. So in this context, it is very important to counter Drug-Drug Interactions (DDIs).

Aim: To assess, compare and compile DDIs of HCQ with other medications and their risk management. Software databases like Lexicomp, drugs.com DDI checker and Medscape DDI checker were utilized to obtain various spectrum of DDIs.

Materials and Methods: The study was undertaken in Department of Pharmacology from 31st March 2020 to 30th April 2020, in a Tertiary Care Teaching Hospital in Eastern India. This was an observational, software-based study. Lexicomp® drug Interactions software was the baseline software, used to access the details of DDIs of HCQ like severity, adverse effects, types of DDIs, risk management of DDIs and their reliability. Drugs.com and Medscape interaction checkers were used to compare details of DDIs obtained from Lexicomp. Spearman's rank order correlation and reliability (cohen's kappa) of the data obtained from the three software programs were analysed.

Results: Total number of DDIs of HCQ with individual drugs were found to be 279. Among these DDIs of individual drugs, maximum risk rating of C (66.66%). The adverse effect that was maximum reported in Lexicomp was changes in glycaemic control whereas Medscape and drugs.com software programs showed QT prolongation. Considering Lexicomp as standard, the correlation with Medscape and Drugs.com interaction checker software programs were -0.257 (weakly negative) and -0.359 (moderately negative), respectively. When Medscape and drugs.com were compared, both showed strong positive correlation (r=0.716). Cohen's kappa between Lexicomp and Medscape, Lexicomp and drugs.com, Medscape and drugs.com were 0.011 (slightly reliable), 0.004 (poorly reliable), 0.568 (moderately reliable), respectively.

Conclusion: There is a need to improve knowledge and awareness amongst the treating physicians and the healthcare professionals of HCQ related DDIs in the higher risk cases especially related to COVID-19 or for prophylaxis and/or other. It was observed that Lexicomp software is better in assessing DDIs of HCQ as compared to other two software programs.

Keywords: Drugs.com, Glycaemic control, Lexicomp, Medscape

INTRODUCTION

The upsurge of the COVID-19 pandemic has spurred an enormous global effort to develop novel molecule in early clinical trials, repurposing the already existing drugs as well as develop new vaccines. This virus belongs to genera beta-coronavirus, which also includes Severe Acute Respiratory Syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV) [1].

HCQ inhibits SARS-CoV-2 infection efficiently in vitro cell lines [2]. As a weak base, it elevates the pH of acidic intracellular organelles essential for membrane fusion, therefore inhibits the entry step and the postentry stages of SARS-CoV-2 [2]. As on 03.05.2020, a total of 10,46,450 samples have been tested in India [3]. According to the other sources, among 42,505 confirmed cases, 29,335 are active, 11,775 recovered and 1,391 diseased, showing case fatality rate of 3.27% till 14.04.2020 [4].

HCQ is 4-Aminoquinoline derivative and racaemic mixture consisting of an R and S enantiomer [5]. It is widely used in the treatment of uncomplicated malaria, Rheumatoid Arthritis (RA), chronic discoid lupus erythematosus, systemic lupus erythematosus and photosensitivity diseases. It has also been suggested as an effective treatment for COVID-19 because of its anti-inflammatory and antiviral effects [6,7]. The drug accumulates extensively in the liver and leucocytes. Hence, concentrations are higher in whole blood than in plasma or serum [8]. A 200 mg oral dose has a $t_{1/2}$ of 22.4 days in blood and 123.5 days in plasma [5,6]. There is evidence of higher inter-individual variation in blood concentrations after similar doses in RA patients. The slow elimination, variable Pharmacokinetic (PK) lead to delayed and variable clinical response. This variation may arise partly from genetic differences to metabolise HCQ through CYP2C8, CYP3A4/5, and CYP2D6 [8].

The empirical evidence for the effectiveness of HCQ/CQ in COVID-19 is currently very meagre. A study in France conducted with small sample size, showed that HCQ alone or in combination with azithromycin, shortened the time to resolution of viral shedding of COVID-19 [9]. Based on this limited data, the national task force for COVID-19, India recommends the use of HCQ for prophylaxis based on risk benefit analysis in high risk population [10]. As per recent revised national clinical management guideline for COVID-19, Government of India, recommends use of HCQ in combination with azithromycin under medical supervision in patients with severe disease and requiring ICU management [11].

In this context, it is very imperative to counter DDIs of HCQ with respect to other drugs if concurrently being administered due to one or more comorbidities. DDIs may be life threatening in prophylactic dose as well as in COVID-19 patients. Many a times the potentially harmful effects are due to DDIs, which may contribute to the added morbidity and mortality of patients as well as hampers the ease of management by the clinicians. To the best of our knowledge, there is limited published data supporting DDIs of HCQ before the recent surge in HCQ use in managing COVID-19 infections. Though data regarding DDIs is available in evidence based software programs, but many treating physicians either do not have knowledge about the software or they don't have the access to it.

Hence, the aim of the study was to assess, compile and classify the DDIs of HCQ for the ease of healthcare professionals using standard DDI software programs like Lexicomp, Drugs.com DDI checker and Medscape DDI checker and their risk management.

MATERIALS AND METHODS

A prospective observational study was undertaken in Department of Pharmacology from 31st March 2020 to 30th April 2020, in a tertiary care teaching hospital in eastern India.

Lexicomp® Drug Interaction software powered by Wolters Kluwer Health, was used as clinical decision support system to assess DDIs of HCQ. This is an online, offline, as well as application based software to check DDIs available on the website- www.uptodate.com [12]. This is basically a paid software (institutional subscription), but trail version can be assessed by any one free for one month. Lexi-Interact is a complete drug and herbal interaction analysis program capable of assessing potential DDIs, drug-allergy interactions and duplicate therapy interactions. It provides the severity, risk rating, reliability, mechanism of DDIs, risk factors/groups if any and the summary of DDIs with references [13].

At first HCQ was searched through the DDI search engine to depict the frequency and spectrum of DDIs with other group of drugs present in the software database. A dependency identifies various factors that may influence the occurrence or severity of the interaction. Reliability rating indicates the quantity and nature of documentation for an interaction. Severity rating indicates the possible magnitude of an interaction outcome [13].

Each DDI is assigned a risk rating from A to X (increased urgency for responding to the data) as shown in [Table/Fig-1] below.

The drug disease interaction was assessed from drugs.com interaction checker, which is available online free of cost. The severity of DDIs those collected from Lexicomp, were compared with drugs.com drug interaction checker as well as Medscape drug interaction checker. Medscape contains a separate tool for detecting DDIs known as the multidrug interaction checker tool. The program lists the possible DDIs and categorises DDIs according to their interaction effect, severity and management on entering the drug one by one [14]. The www.drugs.com drugs interaction checker is powered by four independent leading medical-information suppliers: Wolters Kluwer Health, American Society of Health-System Pharmacists, Cerner Multum and Thomson Reuters Micromedex [15]. Qualitative assessment and classification of severity of DDIs comparison of software programs are depicted in [Table/Fig-2,3]. The drug disease interaction was assessed only from drugs.com interaction checker, which is available online free of cost. As far as qualitative assessment of software programs are concerned, Lexicomp is better in all aspects as depicted in [Table/Fig-2], except the drug disease interactions, which is only present in drugs.com DDI checker.

STATISTICAL ANALYSIS

Severity and adverse effects of DDIs were assessed in frequency and percentage. Comparison of three software programs with respect to severity were analysed to assess Spearman's rank order correlation and reliability (cohen's kappa). Before analysis, severity was assigned with ranks for Lexicomp, drugs.com drug interaction checker and Medscape drug interaction checker as major-major-serious=3, moderate-moderate-significant=2, minor=1, No-no interaction/not found=0.

Risk rating	Action	Description
A	No Interaction	Data have not demonstrated either PK or PD interactions between the specified agents
B	No action needed	Specified agents may interact with each other, but there is little/ no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Modify regimen	A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken to realise the benefits and/or minimise the toxicity resulting from concomitant use. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid combination	The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

[Table/Fig-1]: Risk rating and their management of Lexicomp.
PD: Pharmacodynamic; PK: Pharmacokinetic

Software programs	Severity	Risk rating	Mechanism of interaction	Preventable measures	Duplications of DDIs with different mechanism	Drug-disease interaction	Bibilography to support the data
Lexicomp	Yes	Yes	Yes	Yes, well elucidated	Yes	No	Yes
Drugs.com	Yes	No	Yes	Yes, but not well elucidated	No	Yes	Yes
Medscape	Yes	No	No	Few, nothing understandable	Yes	No	No

[Table/Fig-2]: Qualitative assessment of comparison of software programs.

	Lexicomp [12,13]	Drugs.com [15]	Medscape [14]
Severity	**Major** (effects may result in death, hospitalisation, permanent injury, or therapeutic failure **Moderate** (medical intervention needed to treat effects; effects do not meet criteria for Major) **Minor** (effects would be considered tolerable in most cases- no need for medical intervention)	**Major:** Avoid combinations; the risk of the interaction outweighs the benefit. **Moderate:** Usually avoid combinations; use it only under special circumstances. **Minor:** Minimise risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan. **Unknown:** No interaction information available.	**Contraindicated** **Serious:** Risk of life threatening drug interaction; use alternative drug. **Significant:** Potential for dangerous interaction, use with caution and monitor closely **Minor:** Non-significant interaction.

[Table/Fig-3]: Classification of severity of DDIs comparison of software programs.

RESULTS

When HCQ was searched in Lexicomp drug interaction checker, 33 DDIs were identified in accordance to risk rating. Among these DDIs of HCQ with total number of individual drugs (N=279) listed in Lexicomp, 1.43% had risk rating of X, 1.07% had risk rating of D, 66.66% had risk rating of C and 30.82% had category B as depicted in [Table/Fig-4,5].

The severity of most of the DDIs (N=279) are moderate in nature 188 (67.38%), which includes drugs like androgens, anti-diabetic agents, salicylates, quinolones, SSRIs, azithromycin and drugs having high risk of QT prolongation as depicted in [Table/Fig-4,5] (also refer [Table/Fig-11]). Number of minor interactions are 85 (30.46%) and major interactions are 6 (2.15%). Majority of DDIs among total DDIs (N=279) are PD type {233 (83.51%)} followed by PK/PD type {26 (9.31%)} and PK type {20 (7.16%)}, respectively as depicted in [Table/Fig-4,5]. The possible magnitude of interactions is more in high risk groups/dependencies irrespective of severity as mentioned in Lexicomp and drugs.com drug interaction.

Interaction of HCQ (N=279)	Name of the drugs in the group	Risk rating
Antimalarials (n=3)	Artemether, Lumefantrine, Mefloquine	X
Antivirals (n=1)	Remdesivir	X
Immunosuppressant (n=1)	Cyclosporine	D
Antileprosy agents (n=2)	Dapsone (Systemic), Dapsone (topical)	D
Androgens (n=7)	Fluoxymesterone, Mesterolone, Methyltestosterone, Nandrolone, Oxandrolone, Oxymetholone, Testosterone, Except Danazol	C
Blood glucose lowering effects interacting members (n=68)	Antidiabetic Agents Interacting Members Acarbose, Albiglutide, Alogliptin, Anagliptin, Bromocriptine, Canagliflozin, Chlorpropamide, Dapagliflozin, Dulaglutide, Empagliflozin, Ertugliflozin, Evogliptin, Exenatide, Gemigliptin, Gliclazide, Glimepiride, Glipizide, Glyburide, Insulin (Oral Inhalation), Insulin Aspart, Insulin Degludec, Insulin Detemir, Insulin Glargine, Insulin Glulisine, Insulin Lispro, Insulin NPH, Insulin Regular, Ipragliflozin, Linagliptin, Liraglutide, Lixisenatide, Lobeglitazone, Metformin, Miglitol, Mitiglinide, Nateglinide, Pioglitazone, Pramlintide, Repaglinide, Rosiglitazone, Saxagliptin, Semaglutide, Sitagliptin, Teneligliptin, Tolazamide, Tolbutamide, Vildagliptin, Voglibose Other agents causing hypoglycaemia are Chloroquine, Chlorpromazine, Citalopram, Escitalopram, Disopyramide, Lanreotide, Mecasermin, Mifepristone, Octreotide, Pasireotide, Pentamidine, Perhexiline, Quinine, Somatostatin Acetate, Sulfadiazine, Sulfadoxine, Sulfamethoxazole, Sulfisoxazole, Sunitinib, Tramadol	C
Antipsychotic agents (Phenothiazine) (n=8)	Fluphenazine, Methotrimeprazine, Periciazine, Perphenazine, Prochlorperazine, Promazine, Thioridazine, Trifluoperazine	C
Beta blockers (n=16)	Acetobutolol, Amosulalol, Arotinolol, Betaxolol (Ophthalmic), Bisoprolol, Carvedilol, Celiprolol, Esmolol, Labetolol, Metoprolol, Nebivolol, Oxprenolol, Pindolol, Propramolol, Tertatolol, Timolol (Ophthalmic/systemic) Exceptions Atenolol, Carteolol (Ophthalmic), Levobunolol, Metipranolol, Nadolol, Sotalol	C
Cardiac glycosides (n=2)	Digitoxin, Digoxin	C
Antipsychotic agents (Butyrophenones)	Haloperidol	C
Herbs (n=15)	Alfalfa, Aloe, Bilberry, Bitter Melon, Burdock, Celery, Damiana, Fenugreek, Garcinia, Garlic, Ginger, Ginseng (American), Gymnema, Marshmallow, Stinging Nettle	C
Maitake		C
Monoamine oxidase inhibitors (n=9)	Isocarboxazid, Linezolid, Methylene Blue, Moclobemide, Phenelzine, Rasagiline, Safinamide, Selegiline, Tranylcypromine	C
Growth hormone receptor antagonist	Pegvisomant	C
Antitubercular agent	Prothionamide	C
QT-Prolongation agents (Highest risk) (n=25)	Ajmaline, Amiodarone, Arsenic Trioxide, Astemizole, Bedaquiline, Bepridil, Chlorpromazine, Cisapride, Delamanid, Disopyramide, Dofetilide, Dronedarone, Ibutilide, Ivosidenib, Lenvatinib, Methadone, Procainamide, Quinidine, Quinine, Selpercatinib, Sotalol, Terfenadine, Vandetanib, Vernakalant, Ziprasidone	C
Quinolones (n=13)	Ciprofloxacin (Systemic), Delafloxacin, Gemifloxacin, Levofloxacin (Oral, Inhalation, systemic), Lomefloxacin, Moxifloxacin (Systemic), Nalidixic Acid, Norfloxacin, Ofloxacin (Systemic), Pefloxacin, Pipemidic Acid, Sparfloxacin, Zabofloxacin	C
Salicylates (n=9)	Aminosalicylic Acid, Aspirin, Bismuth Subsalicylate, Choline Magnesium Trisalicylate, Choline Salicylate, Magnesium Salicylate, Salsalate, Sodium Salicylate, Triflusal	C
Selective serotonin reuptake inhibitors (SSRIs) (n=9)	Citalopram, Dapoxetine, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Vilazodone, Vortioxetine	C
Selective Estrogen Receptor Modulator	Tamoxifene	C
Angiotensin converting enzyme inhibitors (ACEIs) (n=6)	Captopril, Enalapril, Lisinopril, Ramipril, Benzapril, Perindopril	B
Immunosuppressant	Methotrexate	B
Antiemetics	Ondansetron (IV Route)	B
Antiparasitic agents (n=2)	Pentamidine (IV Route), Praziquantel	B
Antitubercular agent	Rifampin	B
QT-Prolongation agents (Moderate risk) (n=44)	Amisulpride (Injection), Azithromycin (Systemic), Ceritinib, Chloroquine, Clarithromycin, Clofazimine, Clozapine, Crizotinib, Dasatinib, Domperidone, Doxepin (Topical/systemic), Droperidol, Encorafenib, Entrectinib, Erythromycin (Systemic), Flecainide, Fluconazole, Flupentixol, Gadobenate Dimeglumine, Gemifloxacin, Gilteritinib, Halofantrine, Inotuzumab Ozogamycin, Levofloxacin (Oral, Inhalation, systemic), Lofexidine, Midostaurin, Moxifloxacin (Systemic), Nilotinib, Olanzapine, Osimertinib, Pilsicainide, Pimozide, Piperaquine, Probucol, Propafenone, Quetiapine, Ribociclib, Risperidone, Saquinavir, Sodium Stibogluconate, Sparfloxacin, Thioridazine, Toremifene, Vemurafenib, Voriconazole	B
QT-Prolongation agents (Intermediate risk) (n=31)	Anagrelide, Asenapine, Benperidol, Bromperidol, Buprenorphine, Ciprofloxacin (Systemic), Eliglustat, Fexinidazole (INT), Glasdegib, Iloperidone, Lefamulin (Intravenous), Loperamide Oxide, Lopinavir, Macimorelin, Mizolastine, Norfloxacin, Ofloxacin (Systemic), Oxaliplatin, Paliperidone, Panobinostat, Pazopanib, Pimavanserin, Pitolisant, Promazine, Radotinib, Sulpiride, Telithromycin, Tetrabenazine, Vardenafil, Vinflunine, Zuclopenthixol	B

[Table/Fig-4]: Drugs and group of drugs having DDIs with their risk rating in Lexicomp (N-279).

Sl No.	Interaction of HCQ	Severity	Reliability	Type of DDI	Mode of action of DDIs	Risk group/Dependencies	No. of references to support the data
1	Artemether	Major	Fair	PD?	Addition		1
2	Lumefantrine	Major	Fair	PD?	Addition		2
3	Mefloquine	Major	Fair	PK/PD			3
4	Remdesivir	Major	Fair	PD	Antagonism		1
5	Cyclosporine	Moderate	Poor	PK			2
6	Dapsone (Systemic)	Major	Good	PD		G6PD deficiency, Methaemoglobin reductase deficiency, Haemoglobin M	4
7	Dapsone (topical)	Major	Good	PD		G6PD deficiency, Methaemoglobin reductase deficiency, Haemoglobin M	4
8	Androgens (n=7)	Moderate	Fair	PD		Diabetic patients	25
9	Antidiabetic agents/other blood glucose lowering agents (n=68)	Moderate	Fair	PD		Diabetic patients	15
10	Antipsychotic agents (Phenothiazine) (n=8)	Moderate	Good	PK/PD			1
11	Beta blockers (n=16)	Moderate	Good	PK	Metabolism		4
12	Cardiac glycosides (n=2)	Moderate	Fair	PK			2
13	Citalopram	Moderate	Fair	PD	Additive		13
14	Escitalopram	Moderate	Fair	PD	Additive		12
15	Haloperidol	Moderate	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	9
16	Herbs (n=15)	Moderate	Fair	PD	Additive	Diabetic patients	1
17	Maitake	Moderate	Fair	PD	Additive	Diabetic patients	1
18	Monoamine oxidase inhibitors (n=9)	Moderate	Fair	PK/PD		Diabetic patients	6
19	Pegvisomant	Moderate	Fair	PD	Additive	Diabetic patients	1
20	Prothionamide	Moderate	Fair	PD	Additive	Diabetic patients	2
21	QT-Prolongation agents (Highest risk) (n=25)	Moderate	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	7
22	Quinolones (n=13)	Moderate	Fair	PD		Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Diabetics, Higher drug concentrations	14
23	Salicylates (n=9)	Moderate	Fair	PD		Diabetic patients	15
24	SSRIs (except citalopram, escitalopram) (n=7)	Moderate	Fair	PK/PD		Diabetic patients	14
25	Tamoxifen	Moderate	Fair	PD	Synergism		3
26	ACE Inhibitors (n=6)	Minor	Fair: Inconsistent	PD			17
27	Azithromycin	Moderate	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	12
28	Methotrexate	Minor	Good	PD			1
29	Ondansetron (IV Route)	Minor	Fair	PD			12
30	Pentamidine (IV Route)	Minor	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	12
31	Praziquantel	Moderate	Fair	PK/PD			2
32	Rifampin	Minor	Poor	PK	Metabolism by CYP2D6		1
33	QT-Prolongation agents (Moderate risk) Except Azithromycin (n=44)	Minor	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	7
34	QT-Prolongation agents (Intermediate risk) (n=31)	Minor	Fair	PD	Additive	Older age, Female sex, Bradycardia, Hypokalemia, Hypomagnesemia, Heart disease, Higher drug concentrations	7

[Table/Fig-5]: Qualitative assessment of DDIs in Lexicomp.
*PK=pharmacokinetics, PD=pharmacodynamics, ?=probably, PK/PD=both pharmacokinetics and pharmacodynamics

Most common adverse effect observed due to individual DDIs (N=279) are changes in glycaemic control mostly hypoglycaemia (49.10%) followed by QT prolongation (39.06%) as depicted in [Table/Fig-6] (also refer [Table/Fig-11]).

Risk management of different DDIs is utmost necessary to reduce comorbidities, especially in high risk groups, severely ill patients and those patients having polypharmacy. Risk management of different adverse effects is depicted in [Table/Fig-7].

Sl No.	Interaction of Hydroxychloroquine (N=279)	Adverse effects 1	Adverse effects 2	Adverse effects 3
1	Artemether Limited safety data	Concerns regarding possible QTc prolongation		
2	Lumefantrine Limited safety data	concerns regarding possible QTc prolongation		
3	Mefloquine	QTc prolongation	Risk of convulsions may be increased	HCQ serum concentration is increased
4	Remdesivir	HCQ may diminish the therapeutic effect of remdesivir		
5	Cyclosporine	Cyclosporine serum concentration is increased	Increased ADRs of cyclosporine	
6	Dapsone (Systemic)	Enhance risk of haemolytic reactions		
7	Dapsone (topical)	Enhance risk of haemolytic reactions		
8	Androgens (n=7)	Enhance the hypoglycaemic effect	Insulin resistance with Danazol	
9	Antidiabetic agents/other blood glucose lowering agents (n=68)	Enhance the hypoglycaemic effect		
10	Antipsychotic agents (Phenothiazine) (n=8)	Increase the serum concentration of Phenothiazines	Sedation	QTc prolongation
11	Beta blockers (n=16)	Decreased metabolism of beta blockers by CYP2D6		
12	Cardiac glycosides (n=2)	Inhibition of p-glycoprotein mediated digoxin transport.		
13	Citalopram	Enhance the QTc-prolonging effect of Citalopram	Enhance the hypoglycaemic effect of HCQ	
14	Escitalopram	Enhance the QTc-prolonging effect of Citalopram	Enhance the hypoglycaemic effect of HCQ	
15	Haloperidol	QTc prolongation		
16	Herbs (n=15)	Enhance the hypoglycaemic effect		
17	Maitake	Enhance the hypoglycaemic effect		
18	Monoamine oxidase inhibitors (n=9)	Hydrazine-type MAOIs to potentiate insulin secretion	Release of an ineffective neurotransmitter due to chronic inhibition	Displacement of plasma proteins
19	Pegvisomant	May enhance the hypoglycaemic effect		
20	Prothionamide	Prothionamide may enhance the hypoglycaemic effect		
21	QT-Prolongation agents (Highest risk) (n=25)	May enhance dose dependent QTc prolongation		
22	Quinolones (n=13)	Enhance the hypoglycaemic effect in first few days	May diminish the therapeutic effect after several days	Enhance QTc prolongation (not all as in [Table/Fig-11])
23	Salicylates (n=9)	Enhanced insulin secretion	Reduced hepatic glucose output	Increased insulin sensitisation
24	Selective serotonin reuptake inhibitors (n=7)	Enhance the hypoglycaemic effect	Displacement from protein binding sites	Fluvoxamine inhibits CYP2C99, so sulfonylurea metabolism
25	Tamoxifen	Increase risk of retinal toxicity		
26	Angiotensin converting enzyme inhibitors (n=6)	Enhance the hypoglycaemic effect		
27	Methotrexate	Decrease the serum concentration of Methotrexate		
28	Ondansetron (IV Route)	Enhance the QTc-prolonging effect		
29	Pentamidine (IV Route)	Enhance the QTc-prolonging effect of Pentamidine		
30	Praziquantel	Decrease the serum concentration of Praziquantel		
31	Rifampin	Rifampin may diminish the therapeutic effect of HCQ		
32	QT-Prolongation agents (Moderate risk) (n=44)	Enhance the QTc-prolonging effect		
33	QT-Prolongation agents (Intermediate risk) (n=31)	Enhance the QTc-prolonging effect		

[Table/Fig-6]: Adverse effects due to DDIs in Lexicomp.

Different pathological conditions/comorbidities are depicted from drugs.com interaction checker, which should be considered before initiation of HCQ as depicted in [Table/Fig-8].

Among 279 individual DDIs with different grade of severity reported (in [Table/Fig-11]), number of adverse effect/s per DDI were compared between the software programs in [Table/Fig-9]. The adverse effect that was maximum reported in Lexicomp was changes in glycaemic control whereas Medscape and drugs.com software programs showed QT prolongation as depicted in [Table/Fig-9] (also refer [Table/Fig-11]).

Severity was considered as serious/major in nature maximally by drugs.com (33.33%) and moderate by Lexicomp (69.90%) as depicted in [Table/Fig-10].

Keeping Lexicomp as standard, the Spearman's rank order correlation with Medscape DDI checker was -0.257 ($p<0.001$) (weakly negative) and with Drugs.com DDI checker was -0.359 ($p<0.001$) (moderately

Sl No.	Interaction of HCQ	Risk management
1	Artemether	Avoid combination
2	Lumefantrine	Avoid combination
3	Mefloquine	Avoid concurrent use/maintain 12 hours gap
4	Remdesivir	Concomitant administration is not recommended.
5	Cyclosporine	Monitor for increased serum concentrations/toxic effects of cyclosporine
6	Dapsone (Systemic)	Closely monitor patients for signs/symptoms of haemolytic reactions
7	Dapsone (topical)	Closely monitor patients for signs/symptoms of haemolytic reactions
8	Androgens	Monitor for hypoglycaemia and/or decreased requirements of antidiabetic agents
9	Antidiabetic agents	Monitor patients closely for hypoglycaemic effects if these agents are combined.
10	Antipsychotic agents (Phenothiazine)	Monitor for toxic effects of phenothiazines
11	Beta blockers	Monitor for increased effects of beta-blockers
12	Cardiac glycosides	Monitor for increased serum concentrations/toxic effects of cardiac glycosides
13	Citalopram	Monitor for hypoglycaemia and prolonged QT-interval
14	Escitalopram	Monitor for hypoglycaemia and prolonged QT-interval
15	Haloperidol	Monitor for QTc interval prolongation and ventricular arrhythmias
16	Herbs	Monitor for increased risk of hypoglycaemia
17	Maitake	Monitor for increased risk of hypoglycaemic events
18	Monoamine oxidase inhibitors	Monitor for hypoglycaemia
19	Pegvisomant	Monitor for signs and symptoms of hypoglycaemia
20	Prothionamide	Monitor for hypoglycaemia
21	QT-Prolongation agents (Highest risk)	Monitor for QTc interval prolongation and ventricular arrhythmias (including Torsade de pointes)
22	Quinolones	Monitor for evidence of hypo- or hyperglycaemia
23	Salicylates	Monitor for hypoglycaemia
24	Selective serotonin reuptake inhibitors	Increased monitoring of glycaemic control
25	Tamoxifen	Monitor patients annually for increased risk of retinal toxicity
26	Angiotensin converting enzyme inhibitors	Usually no action needed. If required, then monitor for hypoglycaemia
27	Methotrexate	Usually no action required. If required Methotrexate dose to increase and monitor.
28	Ondansetron (IV Route)	Usually no action required. But ECG monitoring is necessary in high risk groups.
29	Pentamidine (IV Route)	Increased ECG monitoring may be considered
30	Praziquantel	No action required.
31	Rifampin	No action needed. If required HCQ dose should be increased
32	QT-Prolongation agents (Moderate risk)	No action is required for the majority of patients. Increased ECG monitoring may be considered in patients at high risk for QT interval prolongation
33	QT-Prolongation agents (Intermediate risk)	No action is required for the majority of patients. Increased ECG monitoring may be considered in patients at high risk for QT interval prolongation

[Table/Fig-7]: Risk management of adverse effects of DDIs in Lexicomp.

	Interaction of HCQ	Potential Hazard	Plausibility	Adverse effects	No. of References to support the data
1	Oculotoxicity/ Oculopathy	Major	High	Retinal/visual field changes	8
2	Porphyria	Major	Moderate	Exacerbate the condition	3
3	Bone marrow suppression	Moderate	Low		4
4	Ototoxicity	Moderate	Low	Irreversible nerve type deafness	2
5	Seizure	Moderate	Low	Increase seizure threshold	5
6	Hepatotoxicity	Moderate	Low	Abnormal liver function and fulminant hepatic failure	4
7	Psoriasis	Moderate	Moderate	Precipitate attack	7
8	Heart disease	Moderate	Low	Cardiomyopathy with high daily doses	0

[Table/Fig-8]: HCQ and disease/pathological state interaction in Drugs.com DDI Checker.

	Number of adverse events due to DDIs (N=279)		
Software	0	1	2
Lexicomp	00	263	16
Medscape	196	83	00
Drugs.com	153	126	00
	Number of adverse effects due to DDIs		
Spectrum of adverse effects	Lexicomp (n=279)	Medscape (n=83)	Drugs.com (n=126)
QT prolongation	109	76	103
Changes in glycaemic control	137	00	16
Increase in concentration of either drugs	11	03	01
Haemolytic reaction	02	01	01
Decrease in concentration/ metabolism of either drugs	19	03	02
Retina toxicity	01	00	00
Peripheral neuropathy	00	00	02
Increase risk of seizure	0	0	1

[Table/Fig-9]: Number and spectrum of adverse effect due to DDIs based on software programs.

Software	Severity	Frequency	Percentage
Lexicomp	Major	06	2.20
	Moderate	195	69.90
	Minor	78	28.00
	No interactions	0	0
Medscape	Serious	78	28.00
	Significant	02	0.70
	Minor	03	1.10
	No interactions	196	70.30
Drugs.com	Major	93	33.33
	Moderate	30	10.80
	Minor	04	1.40
	No interactions	152	54.50

[Table/Fig-10]: Frequency of severity based on software data comparison (also documented in [Table/Fig-11]).

negative). If Medscape and drugs.com were compared, both showed strong positive correlation (r=0.716) (p<0.001). Reliability analysis showed that Cohen's kappa between Lexicomp and Medscape, Lexicomp and Drugs.com, Medscape and Drugs.com were 0.011 (p=0.039) (slightly reliable), 0.004 (p=0.750) (poorly reliable), 0.568 (p<0.001) (moderately reliable) respectively as depicted in [Table/Fig-10,11]. As number of DDIs observed in Medscape and drugs.com DDI checker either did not match or did not observed as compared to Lexicomp, correlation and reliability clearly showed weak relationship.

DISCUSSION

Monitoring of the potential side effect linked with QTc-prolongation with more than 170 drugs, is an important challenge in clinical practice [16]. Torsade de pointes (Tdp) is a form of polymorphic ventricular tachycardia associated with heart rate-corrected QT (QTc) interval prolongation. Approximately, 24-61% of critically ill patients experience QTc interval prolongation [17].

Most common DDIs of HCQ, as reported from all the three software databases, are QTc prolongation which can lead to Tdp and cardiac arrhythmia. Among the three softwares, Lexicomp classified QTc as high risk, moderate risk and intermediate risk, which is not observed in other two software programs. Antipsychotics-diphenylbutylpiperidine (pimozide), antipsychotics-butyrophenones (haloperiodol, benperidol, bromperidol), antipsychotics-phenothiazines (fluphenazine, methotrimeprazine, periciazine, perphenazine, prochlorperazine, promazine, thioridazine, trifluoperazine), antipsychotics thioxanthine (Zuclopenthixol), antipsychotics atypical (quetiapine, paliperidone, pimavanserin, Sulpiride), antihistaminics (astemizole, terfenadine, mizolastine), antitubercular agent (prothionamide, bedaquiline, delamanid), opioid analgesics (methadone), prokinetic agents (cisapride) most of the betablockers have higher risk of increased QTc in accordance to Lexicomp, which is similar to many research articles [18-22]. Drugs.com DDI checker showed that all above drugs except pimozide, quetiapine, benperidol, prothionamide has increased risk of QTc prolongation. Medscape.com DDI checker showed that all above drugs except pimozide, quetiapine, benperidol, bromperidol, periciazine. perphenazine, promazine, thioridazine, prothionamide, delamanid, cisapride has increased risk of QTc prolongation. Comparison of drugs causing moderate and intermediate risk QTc in Lexicomp with other two software are depicted in [Table/Fig-11]. Several guideline panels, including the American College of Cardiology, recommend that patients with COVID-19, treated with HCQ discontinue any non-critical drugs that can prolong the QT interval [18-22].

Signs/symptoms of hypoglycaemia has been observed in diabetic/non-diabetic patients receiving HCQ [22]. HCQ may enhance the effects of a hypoglycaemic treatment, which requires a decrease in doses of insulin or anti-diabetic drugs [23]. Enhanced/changes in glycaemic effect is observed as DDIs in Lexicomp with other group of drugs like androgens, antiprogestrogens, recombinant human IGF1 (mecasermin), somatostatin analogues, adrenergic receptor antagonist (lofexidine), antibacterials (sulfonamides, quinolones, antileprotics, macrolides, ketolides, oxazolidinones) antiretrovirals (saquinavir, lopinavir), antidepressants (mostly MAO inhibitors, selective serotonin receptor inhibitors), antiarrhythmic class Ia, Ic, III [24,25], which is not depicted in Drugs.com and Medscape DDI checker software programs as shown in [Table/Fig-9].

In many instances, increased serum concentration and in turn adverse reactions of cardiac glycosides (as observed in all the three software programs), immune-suppressants like cyclosporine (as observed in Lexicomp, Medscape.com but not in Drugs.com DDI checker) was reported by inhibiting p-glycoproteins [19,20,26]. Decrease in concentration of methotrexate can lead to failure of therapeutic effect as a result of DDIs as observed in all the three software programs. When severity is of major type, it is always recommended to avoid combination and in moderate cases, should be monitored properly, but risk-benefit should be considered in both cases. Elderly, female gender, patients on anti-diabetics medication, congenital long QT prolongation, increased drug concentration, cardiac disease, electrolyte imbalances (hypokalemia, hypomagnesemia etc.,) are always at high risk irrespective of severity of DDIs [13,15,21]. Chloroquine analogues may also lower the seizure threshold (as per [Table/Fig-5]), which may interact with the antiepileptic agents [18].

HCQ may diminish the therapeutic effect of Remdesivir. The fact sheet for healthcare professionals for the emergency use authorisation of remdesivir states that in vitro data suggest that chloroquine/HCQ exhibits an antagonistic effect on the intracellular metabolic activation and antiviral activity of remdesivir. Due to this antagonism observed in vitro and the possibility of reduced efficacy of remdesivir, concomitant use of remdesivir and HCQ is not recommended [27].

According to one study conducted by Namazi S et al., Lexi-Interact provided most accurate software programs and is a competent, complete and user friendly software [28]. According to two other studies, Lexicomp is very much helpful in assessing DDIs in hospitalised [29] and elderly cancer patients [30]. Another study conducted by Farooqui R et al., showed that drugs.com and medscape.com are the two software programs used and very much helpful in identifying adverse events due to DDIs in medicine outpatient setting [31]. It was observed that Lexicomp software is better as compared to other two software programs as more numbers of data regarding the DDIs based on evidence are available in Lexicomp and qualitatively better as showed in [Table/Fig-2].

DDI software programs are very helpful in assessing and differentiating adverse drug reaction from adverse events due to DDIs, so helpful in clinical management and in turn, helpful in decreasing the morbidity and mortality. There is a need to improve knowledge and awareness of DDIs related issues amongst treating physicians especially related to COVID-19 cases or for prophylaxis, rheumatologists, dermatologists and/or other healthcare professionals performing software tool intervention.

Limitation(s)

Comparing with more number of software could have given more information regarding the DDIs. However, it is a cumbersome task that too many software are not freely available and there are limitations to access as well.

CONCLUSION(S)

Lexicomp is a better software as compared to Drugs.com and Medscape DDI checker, in terms of detecting and assessing adverse events due to DDIs of HCQ. There is a substantial risk of DDIs with HCQ therapy, which can lead to various potentially harmful events and therapeutic failure among patients undergoing HCQ therapy. Furthermore, higher risk group of patients are at

additional risk of adverse consequences. The data will help to aid in decision making during this critical time for healthcare professionals and patients in providing better care for the patients who are in need of this medication.

Note: For economy of space [Table/Fig-11] (9 pages) has been included in online version only. Please refer to URL: https://jcdr.net/articles/supplementarydata/14392/45273_Supplementary_Table_11.pdf.

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