



Original Article

Adverse Drug Reaction (ADR) of Hydroxychloroquine(HCQ) in the -Preexposure Prophylaxis (PrEP) of COVID-19 in Health Care Professionals in a Tertiary Care Teaching Hospital**Pranav S Jadhav^{1,*}, Saleem B Tamboli², Rahul B Parsode³**¹ Assistant Professor, Dept of Pharmacology, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, India² Professor and Head, Dept of Pharmacology, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, India³ Assistant Professor, Dept of Pharmacology, Dr Shankarrao Chavan Government Medical College, Nanded, India

ARTICLE INFO

Article history:

Received 01.12.2023

Accepted 28.12.2023

Published 30.12.2023

* Corresponding author.

Pranav S Jadhav

pranav.jadhav37@gmail.com[https://doi.org/](https://doi.org/10.18579/jopcr/v22.4.72)

10.18579/jopcr/v22.4.72

ABSTRACT

In December 2019 an outbreak of emerging COVID-19 due to the SARS CoV-2 infection started in Wuhan, China and rapidly spread throughout the world. WHO declared COVID-19 as PANDEMIC on 12th March 2020. Various drugs were introduced to treat and prevent this pandemic. Hydroxychloroquine gained widespread attention due to its antiviral action and inhibitory effect. HCQ was preferred which has antiviral effect similar to that of Chloroquine. ICMR and FDA has advocated their use in severe COVID-19 disease. There are uncertain and limited data to support the beneficial effect of this drug. Our study was aimed to investigate the adverse drug reaction of HCQ given prophylactically for COVID-19 to the health care professional. After taking ethical committee approval, a study was conducted among the health care professional from 1st April 2020 to 31st May 2020. The participants were given an online pretested, validated questionnaire to ascertain the adverse effects while taking HCQ. Due to the nature of COVID-19 and restrictions on personal interview and examination, only online symptom questionnaire for adverse effects was given. 183 participants were involved in the study who were working as a health care professional in COVID-19. Out of these 9 participants were excluded based on the exclusion criteria. 73 adverse drug reaction were found in 56 participants. Most common and frequent side effects were headache, nausea, loose stools and dizziness. Almost 22 participants required some painkillers to treat the adverse effects. Data was entered in MS Excel and presented in the form of frequencies and percentages. Almost 32.18% reported adverse effects. So utmost care should be taken before using HCQ prophylactically in health care professionals working in COVID-19.

Keywords: Adverse Drug Reaction; Preexposure Prophylaxis; COVID 19; Hydroxychloroquine; Health Care Professionals

INTRODUCTION

Adverse drug reaction is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"¹. The Thalidomide disaster in 1961 was the start of establishing the WHO Program for International Drug Monitoring, WHO promotes Pharmacovigilance at the country level by working in collaboration with the Monitoring Centre at Uppsala. More than 135 countries are the part of this program. This program not only

enhances patient safety for use of medicines but also gives information about safe use and prevention and treatment of any Adverse Drug Reactions (ADRs). ADRs are responsible for significant morbidity and mortality^{2,3}.

An unprecedented outbreak of pneumonia of unknown etiology in Wuhan City, Hubei province in China emerged in December 2019. A novel coronavirus was identified as the causative agent⁴. WHO declared COVID 19 as PANDEMIC on 12th March 2020 posing a high risk to countries with vulnerable systems⁵. Hydroxychloroquine(HCQ) is a 4-aminoquinoline with immunosuppressive, antiautophagy and antimalarial activities. Initially it was used as anti-

malarial drug and it further extended to use in treatment of chronic rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. HCQ was permitted by US Food and Drug Administration (FDA) and it is also advocated by Indian Council of Medical Research (ICMR) as preexposure prophylaxis for health care professional as well as high risk for household contacts who were in direct contact with the positive patient^{3,4}.

There were many hotspots of COVID-19 which gave an idea to ICMR to start the strategy of giving HCQ prophylactically to all the high-risk community in COVID-19 positive area. So, whenever we give drug in community setting as prophylaxis, several problems may arise including risk of adverse reactions and its monitoring⁶. The data published by ICMR on assessment of HCQ prophylaxis among 1323 HCWs indicated mild adverse effects such as headache, nausea, abdominal pain, vomiting, hypoglycaemia and some cardiovascular effects⁷. However, data to support the use of HCQ and CQ for COVID-19 are limited and inconclusive⁸. FDA has given HCQ as "Emergency use authorization" (EUA) so it was therefore ideal to document and analyse the adverse reaction after taking HCQ prophylactically. In this study we aimed to study the ADR of HCQ in prophylactic doses for COVID-19 among the health care professionals.

MATERIAL AND METHODS

Setting of the study

The present study was conducted from 1st April 2020 to 31st May 2020 on 183 participants from Dr SC GMC and Hospitals, Nanded, Maharashtra in whom the HCQ was given as preexposure prophylaxis for COVID-19 among health care professionals. The ICMR recommended drug HCQ for preexposure prophylaxis in COVID 19 was 400mg orally weekly for 8 weeks to be taken with meals. The participants were chosen from both gender and of age group 18-60 years. Ethical clearance was obtained from the Institutional Ethics Committee prior to the initiation of the study and written informed consent was taken from the participants.

Study Design

It was a prospective observational study of the preexposure prophylaxis of HCQ in COVID 19 for health care professionals. Total 183 participants were included in the study.

Inclusion Criteria

1. Healthy male and non-pregnant and non-lactating females working as a frontline worker in COVID-19
2. Participants who are negative for COVID 19 or not tested
3. Age group 18-60 years

4. Participants taking hydroxychloroquine as preexposure prophylaxis in COVID-19
5. Signed informed consent prior to the study and the participants should fully agree with the content, process and be able to communicate well with the researcher.

Exclusion Criteria

1. Persons who tested COVID positive or whose reports are awaited
2. Persons having allergy to the analogues of the drug
3. Pregnant and lactating females
4. Persons taking any medication including prescribed drugs, over the counter drugs or any other alternative medications (herbal, ayurvedic, or any health supplements)

Withdrawal criteria

Health care professional who denies participation after giving written informed consent.

Study tools

- Details about various demographic information were taken.
- Also data regarding number of doses taken, need for treatment of ADRs and suspected ADRs from the patient were collected.
- The participants were given an online pretested, validated questionnaire to ascertain the adverse effects while taking HCQ.
- Due to the nature of COVID-19 and restrictions on personal interview and examination, only online symptom questionnaire for adverse effects was given.

Statistical Analysis

- The Sample size was calculated as number of health care professionals taking HCQ as Preexposure prophylaxis in COVID-19.
- Accordingly, 183 participants were recruited out of these 9 participants were excluded based on the exclusion criteria.
- Considering this, total sample size was 174.
- Data was entered in MS-Excel version and presented in the form of frequencies and percentages.

RESULTS

- 183 Health care professional working in COVID-19 of age group 18-60 years were included in the study.
- Out of these 9 participants were excluded based on the exclusion criteria

- Out of total participants, 59 participants were with comorbidities with most common being hypertension followed by diabetes.
- Also, there was a male preponderance and the majority of the participants were between 30 and 50 years of age.
- Almost 73 adverse drug reactions were found in 56 participants.
- Most common and frequent side effects were headache, nausea, loose stools and dizziness.
- Almost 22 participants required some medication to treat the adverse effects.

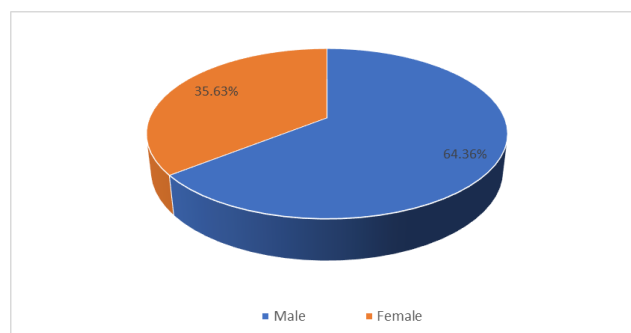


Fig. 1: Gender distribution (n=174)

Table 1: Preliminary data of participants involved in study and received Hydroxychloroquine (n=174)

Characteristic	Number
• Age in years (Median)	
<30	26
30-50	103
>50	45
• Gender	
Male	112
Female	62
• Comorbidities	
Hypertension	34
Diabetes	11
Ischaemic heart disease	4
Kidney disease	2
Liver disease	2
Others	6

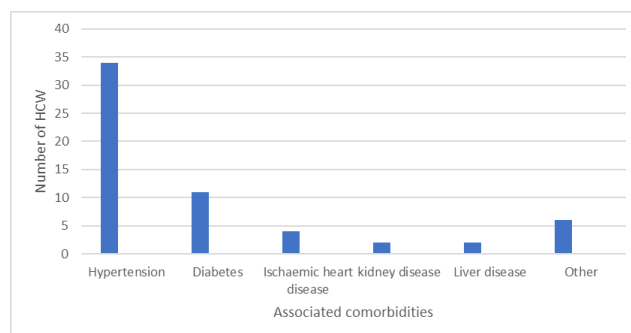


Fig. 2: Associated Comorbidities (n=59)

Table 2: Suspected adverse drug reactions in participants involved in the study received Hydroxychloroquine

Adverse drug reaction	Number
Headache	40
Nausea	17
Loose stools	12
Abdominal cramps	8
Blurred vision	5
Hypoglycemia	4
Vomiting	3
Tinnitus	3
Rash	1
Emotional changes	1
Alopecia	1
Pruritus	1
Total	108

DISCUSSION

Hydroxychloroquine is widely used antimalarial and autoimmune disease drug. Recently, Chloroquine has been reported as a broad-spectrum antiviral drug. At present no effective treatment or vaccine is available for COVID-19. FDA has given EUA for some of the drugs for its use in pandemic and HCQ was one of them for which WHO gave EUA for its use in preexposure prophylaxis as well as for treatment of positive Covid patient. HCQ was also approved by ICMR for the chemoprophylaxis for COVID-19 for the health care professionals working in COVID-19 cases and also for the high risk contacts. There are very limited clinical trials that studied the possible antiviral effect and efficacy of HCQ in treatment of COVID-19 participants⁹⁻¹¹. Also, there was insufficient data available in published literature regarding the safety and efficacy of HCQ as preexposure prophylaxis.

The CDC panel did not recommend using a high dosage of the drug (i.e. 600 mg twice daily for ten days), because increasing the dose may have unwanted adverse outcomes that should be carefully monitored. These doses were higher than recommended for malaria chemoprophylaxis, and clinical trials are needed to establish safety and efficacy¹². However, some adverse drug reaction may not be due to the direct effect of the drug. It can be due to the stressful condition of working in COVID or it can be due to the dehydrating condition in PPE or due

Table 3: Most common suspected adverse drug reactions seen in relation to the age

Adverse drug Reaction		Age group		Total	Chi square value	P value
		< 50 years	> 50 years			
Headache	Present	35	5	40	4.83	0.027 *
	Absent	94	40	134		
Nausea	Present	13	4	17	0.05	0.81
	Absent	116	41	157		
Loose stools	Present	10	2	12	0.56	0.45
	Absent	119	43	162		
Dizziness	Present	9	2	11	0.36	0.54
	Absent	120	43	163		
Abdominal cramps	Present	7	1	8	0.78	0.37
	Absent	122	44	166		

In this table we have taken the age group as <50 years and >50 years of age to determine ADR in relation to the age

(* - Significant P value)

to some drug-drug interactions. Also, HCQ can cause severe hypoglycemia including loss of consciousness that could be life threatening in participants treated with or without antidiabetic medications. So, blood sugar of such participants and drug-drug interactions should be closely monitored by physicians in such vulnerable individuals. A systematic review study done by Xabier Garcia Albeniz et al showed that a low rate of serious adverse effects comprised mainly of mild gastrointestinal side effects¹³. Age more than 50 years and with comorbidities are risk factors for severe adverse drug reactions, so these participants should be closely monitored while giving HCQ. A similar study was done by Elettra Fallani MSc et al. reported that most frequent ADRs reported in 2020 were diarrhea, prolonged QT interval, and hypertransaminasemia which was significantly higher than 2019 and specific for COVID-19 subjects treated with hydroxychloroquine¹⁴.

In our study, as shown in Figure No.1 and Table No. 1, we included 174 participants of age groups <30, 30-50, >50 years of age. Out of this 112 were males and 62 females. Figure No.2 shows the associated comorbidities of the participants. Table No. 2 and 3 showed that headache was the most common adverse drug reaction and it was significant in the age group of less than 50 years of age. There is no such reliable or sufficient data that this headache is due to the HCQ itself due to the limitations of our study which included a small sample size for the adverse drug reactions. Also this study cannot be generalized to the general public even though it may be expected that health care professionals are more aware of the symptoms and are likely to report even the slightest of adverse drug reaction correctly. Some additional staff training on pharmacovigilance, institution of a detailed questionnaire to elicit only relevant adverse drug reactions is needed. So, to ensure the safety and efficacy of HCQ larger studies with big sample size for the preexposure prophylaxis among the health care professionals and with high-risk contacts should be carried out. However, if we take

the treatment part of HCQ in COVID-19, many studies have been done to prove its effectiveness in the pandemic time. A study done by Mirjam Hempenius concluded that the quality of observational studies done to prove the effectiveness of HCQ for the treatment of COVID-19 symptoms was heterogeneous. In high unmet medical needs, where the pandemic hits the general public, observational studies have always been the sole tool to provide timely evidence which are valuable but provided that the evidence is of high quality¹⁵.

CONCLUSION

Almost 1/3rd of the participants reported adverse effects. So utmost care should be taken before using HCQ prophylactically in health care professionals working in COVID-19.

REFERENCES

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*. 2000;356(9237):1255–1259. Available from: [https://doi.org/10.1016/S0140-6736\(00\)02799-9](https://doi.org/10.1016/S0140-6736(00)02799-9).
2. World Health Organization. Safety of Medicines. Guide to Detecting and Reporting Adverse Drug Reactions. Geneva, Switzerland: WHO. Geneva, Switzerland. 2002. Available from: http://www.who.int/hq/2002/WHO_EDM_QSM_2002.2.
3. Moore N, Lecomte D, Noblet C, Mabilie M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *British Journal of Clinical Pharmacology*. 1998;45(3):301–308. Available from: <https://doi.org/10.1046/j.1365-2125.1998.00667.x>.
4. Dietz L, Horve PF, Coil DA, Fretz M, Eisen JA, Van Den Wymelenberg K. 2019 Novel Coronavirus (COVID-19) Pandemic: Built Environment Considerations To Reduce Transmission. 2019. Available from: <https://doi.org/10.1128/mSystems.00245-20>.
5. Lai CCC, Shih TPP, Ko WCC, Tang HJJ, Hsueh PRR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*. 2020;55(3):105924–105924. Available from: <https://doi.org/10.1016/j.ijantimicag.2020.105924>.

6. Kulkarni RK, Kinikar AA, Jadhav T. Adverse Drug Reaction Profile of Prophylactic Hydroxychloroquine for COVID-19 Among Doctors. . Available from: https://journals.lww.com/mjdy/fulltext/2020/13030/adverse_drug_reaction_profile_of_prophylactic.7.aspx.
7. and MD. The ICMR bulletin on targeted hydroxychloroquine prophylaxis for Covid-19: Need to interpret with caution. vol. 19. . Available from: <https://doi.org/10.20529/IJME.2020.040>.
8. Yazdany J, Kim AH. Use of hydroxychloroquine and chloroquine during the COVID-19 pandemic: what every clinician should know. 2020. Available from: <https://doi.org/10.7326/M20-1334>.
9. Gautret P, Lagier J, Parola P, Hoang VT, Meddeb L, Mailhe M. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. 2020. Available from: <https://doi.org/10.1016/j.ijantimicag.2020.105949>.
10. Chen Z, Hu J, Zhang Z, Jian S, Hang S, Yan D. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. 2020. Available from: <https://doi.org/10.1101/2020.03.22.20040758>.
11. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. 2020. Available from: <https://doi.org/10.1136/bmj.m1849>.
12. Al-Kofahi M, Jacobson P, Boulware DR, Matas A, Kandaswamy R, Jaber MM. Finding the Dose for Hydroxychloroquine Prophylaxis for COVID-19: The Desperate Search for Effectiveness. 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32344449/>.
13. García-Albéniz X, Amo JD, Polo R, Morales-Asencio JM, and MAH. Systematic review and meta-analysis of randomized trials of hydroxychloroquine for the prevention of COVID-19. *European Journal of Epidemiology*. 2022;37(8):789–796. Available from: <https://pubmed.ncbi.nlm.nih.gov/35943669/>.
14. Fallani E, Cevenini F, Lazzerini PE, Verdini A, Saponara S. Off-Label Use of Hydroxychloroquine in COVID-19: Analysis of Reports of Suspected Adverse Reactions From the Italian National Network of Pharmacovigilance. *The Journal of Clinical Pharmacology*. 2022;62(5):646–655. Available from: <https://pubmed.ncbi.nlm.nih.gov/34802170/>.
15. Hempenius M, Bots SH, Groenwold RHH, De Boer A, Klungel OH, Gardarsdottir H. Bias in observational studies on the effectiveness of in hospital use of hydroxychloroquine in COVID19. *Pharmacoepidemiology and Drug Safety*. 2023;32(9):1001–1011. Available from: <https://doi.org/10.1002/pds.5632>.