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Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine

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ABSTRACT

Background: Combinations of hydroxychloroquine (HCQ) and azithromycin have been promoted as treatments for COVID-19 based on small, uncontrolled clinical trials that have not assessed potential risks. Risks of treatment include QT segment prolongation, Torsades de Pointes (TdP), and death. This comparative pharmacovigilance analysis evaluated the risk of these events.

Methods: Data from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) (> 13 million total reports) were used. Queries extracted reports based on exposures of HCQ/chloroquine (CQ) alone, azithromycin alone, HCQ/CQ + azithromycin, amoxicillin alone, HCQ/CQ + amoxicillin alone. Amoxicillin served as a control. Events of interest included death and TdP/QT prolongation as well as accidents/injuries and depression as control events. Proportional Reporting Ratios (PRR) and 95% confidence intervals (CI) were calculated where a lower limit of the of 95% CI (Lower95CI) value of ≥2.0 is interpreted as a potential safety signal.

Results: Lower95CIs for HCQ/CQ alone showed no potential safety signals for TdP/QT prolongation, death, or any of the control events included. The PRRs and 95% CIs for TdP/QT prolongation was 1.43 (1.29–2.59) with HCQ/CQ use alone and 4.10 (3.80–4.42) for azithromycin alone. For the combined HCQ/CQ + azithromycin group, the PRR and 95% CI was 3.77 (1.80–7.87). For the control of amoxicillin, there were no safety signals when used alone or in combination with HCQ/CQ.

Conclusions: HCQ/CQ use was not associated with a safety signal in this analysis of FAERS data. However, azithromycin used alone was associated with TdP/QT prolongation events and should be used with caution.

Introduction

Hydroxychloroquine (HCQ) has been promoted as a potential treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its presentation as COVID-19 disease.[1,2] HCQ has several possible mechanisms of action that may promote its use as an antiviral against SARS-CoV-2 via reductions in virus entry and replication as well as immunosuppressive effects to mitigate cytokine storm in severe disease.[2–4] Ongoing trials aim to investigate the effectiveness of HCQ amidst the SARS-CoV-2 pandemic, primarily in patients with decompensating COVID-19.

Meanwhile, current evidence for its use in SARS-CoV-2 and COVID-19 is inconclusive in terms of both efficacy and safety. An uncontrolled clinical study in France (March 2020) reported promising results with HCQ and azithromycin therapy for 22 COVID-19 cases.[5] This study sparked intense attention from the media about the potential of HCQ and chloroquine (CQ) alone or in combinations with azithromycin. Both drugs have shown antiviral and immunosuppressive activity in in-vitro studies,[6,7] which has led to widespread but so far unfounded claims not only for treatment but also for prevention. Medical professionals have cautioned against concomitant use due to a lack of evidence and safety concerns. These safety concerns have primarily centered on the risk of drug-induced QT interval prolongation, which can lead to tachycardias such as Torsades de Pointes (TdP) and sudden cardiac death.[8]

Risk of QT prolongation and TdP has been reported for both HCQ/CQ and azithromycin when used alone.[9,10] However, whether or not the combined use of these medications could lead to additive or synergistic effects on QT prolongation is unknown. In the absence of direct safety data for COVID-19 patients, the purpose of this analysis was to assess the disproportionality in reporting of TdP and QT prolongation for

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these medications when used alone and in combination.

Methods

Public data files from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from the years 1969 through Q3/2019 were used.[11,12] FAERS reports include adverse drug events reported to the agency via mandatory reporting by biopharmaceutical company and voluntary consumer reporting. Each report includes suspected medications, adverse events mapped to MedDRA (Medical Dictionary for Regulatory Activities; meddra.org) terminology, outcomes (e.g. death, hospitalization, etc.), concomitant medications, and other patient information.

Each FAERS report was identified to be mutually exclusive based on the following observed drug mentions: HCQ/CQ alone, azithromycin alone, HCQ/CQ + azithromycin, amoxicillin alone, HCQ/CQ + amoxicillin. Amoxicillin served as a "control" for relative comparisons as FAERS does not facilitate direct comparisons between medications. Amoxicillin is often used for sinusitis and other upper respiratory tract infections similar to azithromycin and has not been associated with QT prolongation effects.[9]

The main adverse events of interest were death and TdP/QT prolongation. To capture each adverse drug event, Standardized MedDRA Queries (SMQ) were utilized, which aggregate MedDRA "Preferred Terms" into meaningful broader categories. To further increase confidence in the results, the analyses also included SMQs for "dummy" outcomes of accidents/injuries and depression as these unrelated medical conditions or events should not be affected by possible drug-drug interaction effects.

A structured query captured all FAERS reports that included HCQ/CQ, azithromycin, or amoxicillin. The query allowed for misspellings using "sound alike" functions in SAS software for both U.S. and international generic and trade names. Initially extracted drug names were manually inspected by the study team to develop the final query.

For each drug group, 2x2 contingency tables were used to calculate the Proportional Reporting Ratio (PRR) based on binary exposures (yes/no) and binary outcomes (yes/no) (Fig. 1).[13] The PRR measures the disproportionality of the outcome in the exposed compared to the unexposed. In FAERS, the unexposed are representative of all other FAERS reports. PRRs are interpreted as being potentially meaningful in pharmacovigilance based on the lower level of the 95% confidence interval (Lower95CI) ≥ 2.0.[14–16] Values less than that are often deemed not to indicate a potential safety signal. Comparative treatment groups are visually inspected for overlap as an assessment of potential biases in reporting. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Over 13.3 million FAERS reports were analyzed. The frequencies of reported adverse events for each study drug are reported in Table 1. Lower95CIs for HCQ/CQ alone showed no potential safety signals for TdP/QT prolongation, death, or any of the control events included (Table 2). Specifically, the Lower95CI for TdP/QT prolongation was 1.29 with HCQ/CQ use alone. For azithromycin, there was a significant safety signal detected with an Lower95CI of 3.80 for TdP/QT prolongation. No other events were significant for the azithromycin group. For the combined HCQ/CQ + azithromycin group (n = 600 total reports), the Lower95CI was 1.80 with a wide confidence interval range. For amoxicillin as a control comparison, there were no safety signals when used alone or in combination with HCQ/CQ.

	Outcome	
Exposed	Yes	No
Yes	A	B
No	C	D

$$PRR = \frac{A \div (A+B)}{C \div (C+D)} \qquad 95\%\ CI = e^{\ln(PRR) \pm 1.96 \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} + \frac{1}{c+d}}}$$

Fig. 1. Example of a 2x2 contingency table and calculation of Proportional Reporting Ratios (PRR) and 95% Confidence Intervals.

Discussion

Although multiple ongoing trials are investigating the efficacy of HCQ alone or in combination with azithromycin, safety concerns are often not resolved in small scale clinical studies. Therefore, monitoring of spontaneous reporting systems is necessary to ensure the safety of repurposed or novel therapeutic options. No significant safety signals were observed for HCQ/CQ when used alone using a disproportionality analysis approach with FAERS data. However, when azithromycin was used alone, it was associated with a significant safety signal related to TdP/QT prolongation. With HCQ/CQ + azithromycin, results did not reach the threshold to indicate a significant safety signal which is likely a result of the small number of reports evident in the wide confidence interval range.

These results are consistent with a pre-print report of an analysis conducted in an international distributed data network analysis of electronic health records and claims databases.[17] That analysis showed that short-term treatment with HCQ appears to be safe, whereas the use of HCQ + azithromycin was associated with 15–20% increases in the risks of angina, chest pain, and heart failure along with two times the increase in cardiovascular mortality. Nevertheless, their study design does not elucidate whether the increased risk with HCQ + azithromycin is due to a potential drug-drug interaction or solely the azithromycin adverse effect.

It should be emphasized that neither the current study nor the preprint study mentioned above were conducted in patients infected with SARS-CoV-2. Both studies captured patient populations utilizing these medications for common indications such as lupus and sinus infections. Results from ongoing clinical trials are desperately needed in order to understand the efficacy of HCQ for the prevention and treatment of COVID-19. Further, safety analyses must consider the disposition of the patient as safety outcomes, particularly TdP/QT prolongation, which may be more common in critically ill patients with impaired renal or liver function, electrolyte abnormalities, and other medical conditions.[8]

Several strengths could be mentioned for the present study. First, FAERS database has the capability to capture rare safety events such as TdP/QT prolongation. Second, this analysis was strengthened by including both control drug exposures and control safety events as means to assess potential reporting biases. However, there are some limitations to the analysis inherent to the data source. FAERS safety reports do not include a denominator of medication users, and may not be used to report rates or relative measures between exposure groups. FAERS data are spontaneously reported and subject to reporting biases associated with public knowledge of a safety issue, release of new medications, or masking effects due to imbalance in event reporting associated with other medications.[15,18] However, more recent time periods were excluded since the COVID-19 pandemic in late 2019, and reporting biases are less likely to impact our findings.

Conclusions

In an analysis of FAERS adverse drug event reports, HCQ/CQ appeared not to be associated with a safety signal related to TdP/QT prolongation when used alone. Azithromycin alone or when used with HCQ/CQ was associated with a potential safety signal. From the perspective of this specific adverse drug event, HCQ/CQ use appears to be relatively safe, but further evidence is needed to affirm its effectiveness

Table 1
Exposure groups, number of reports, and number of events observed for each adverse event in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS): 1964 through Q3/2019.

Drug of interest	Adverse event of interest	Number of reports with event
Hydroxychlorquine/Chloroquine (HCQ/CQ), N = 78,848 report	Death	3412
	TdP/QT prolongation	344
	Accidents/Injuries	5488
	Depression	1341
Azithromycin + HCQ/CQ, N = 600 reports	Death	37
	TdP/QT prolongation	7
	Accidents/Injuries	47
	Depression	24
Amoxicillin + HCQ/CQ, N = 863 reports	Death	45
	TdP/QT prolongation	0
	Accidents/Injuries	66
	Depression	30
Azithromycin, N = 53,378 reports	Death	4097
	TdP/QT prolongation	667
	Accidents/Injuries	2530
	Depression	1210
Amoxicillin, N = 103,661 reports	Death	8809
	TdP/QT prolongation	521
	Accidents/Injuries	4340
	Depression	1806

Table 2
Proportional Reporting Ratios (PRR) and 95% confidence intervals (95% CI) for each exposure and event of interest.

Drug of interest	Adverse event of interest	PRR	Lower 95% CI	Upper 95% CI
Hydroxychlorquine/Chloroquine (HCQ/CQ)	Death	0.46	**0.44**	0.47
	TdP/QT prolongation	1.43	**1.29**	1.59
	Accidents/Injuries	1.73	**1.68**	1.77
	Depression	0.97	**0.92**	1.02
Azithromycin + HCQ/CQ	Death	0.66	**0.48**	0.90
	TdP/QT prolongation	3.77	**1.80**	7.87
	Accidents/Injuries	1.94	**1.47**	2.55
	Depression	2.28	**1.54**	3.38
Amoxicillin + HCQ/CQ	Death	0.56	**0.42**	0.74
	TdP/QT prolongation	NA	**NA**	NA
	Accidents/Injuries	1.89	**1.50**	2.38
	Depression	1.98	**1.40**	2.82
Azithromycin	Death	0.81	**0.79**	0.83
	TdP/QT prolongation*	4.10	**3.80***	4.42
	Accidents/Injuries	1.18	**1.13**	1.22
	Depression	1.29	**1.22**	1.37
Amoxicillin	Death	0.9	**0.88**	0.92
	TdP/QT prolongation	1.65	**1.51**	1.79
	Accidents/Injuries	1.04	**1.01**	1.07
	Depression	0.99	**0.94**	1.04

Note: For pharmacovigilance safety signal detection, the lower limit of the 95% CI is often interpreted as significant if ≥ 2. Those values are marked with a asterisk (*).

for COVID-19 and SARS-CoV-2 infection.

CRediT authorship contribution statement

Amir Sarayani: Conceptualization, Methodology, Writing - review & editing. **Brian Cicali:** Methodology, Formal analysis, Writing - review & editing. **Carl H. Henriksen:** Methodology, Formal analysis, Writing - review & editing. **Joshua D. Brown:** Conceptualization, Methodology, Writing - original draft, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2020.04.016.

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