Safety Profile of Hydroxychloroquine Sulfate vs Acetaminophen vs Ibuprofen in Adults: A Literature Review

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Principal Investigator's Statement

I certify that the information provided in this application is complete and accurate.

I understand that as Principal Investigator, I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human participants, and strict adherence to the study protocol and any stipulations imposed by the California Northstate University and Western University Institutional Review Board.

I understand that, should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the human participants' involvement as described in the funding proposal(s), is consistent in principle, to that contained in this application. I will submit modifications and/or changes to the IRB as necessary, in the form of an amendment, to ensure these are consistent.

I agree to comply with all California Northstate University and Western University policies and procedures, as well as with all applicable federal, state and local laws regarding the protection of human participants in research, including, but not limited to:

• Ensuring all investigators, study coordinators, and key study personnel have completed the CITI human subjects training program;
• Ensuring the project is conducted by qualified personnel following the approved application and study protocol;
• Ensuring that orientation, education and in-service sessions take place whenever non research personnel will be contributing data or interventions to the study authorization is obtained when applicable

Huynh Wynn Tran, MD (signed)
Assistant Professor of Medicine
Principle Investigator’s Signature
Date 04/15/2020

By my signature, I certify that I have evaluated this research application for soundness of research design and scientific merit in accordance with departmental policy and the adequacy of facilities and resources.

Data Availability Statement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest:

The authors have no conflicts of interest to declare.

Brief Description:

1. What is already known about this subject?

   Hydroxychloroquine sulfate has been used for decades in the treatment of malaria and autoimmune diseases, such as rheumatoid arthritis and systemic lupus sclerosis. Amid the ongoing coronavirus pandemic, this drug is being explored for the treatment of COVID-19 patients in the ICU. Other medications being used for outpatient treatment of COVID-19 symptoms include acetaminophen and ibuprofen.

2. What this study adds?

   This paper reviews the major adverse events and minor adverse drug reactions of the three medications and contributes to the understanding of the safety hydroxychloroquine sulfate. Our findings indicate that the safety of short-term use of hydroxychloroquine sulfate is comparable to over-the-counter treatments for COVID-19, such as acetaminophen or ibuprofen.

ABSTRACT

Amid the 2020 Coronavirus pandemic, hydroxychloroquine sulfate (brand name Plaquenil or abbreviated HCQ) is being explored as a potential treatment for those affected with COVID-19 disease. Based on a limited in-vitro and anecdotal clinical data, the U.S. Food and Drug Administration (FDA) approved emergency use of hydroxychloroquine sulfate as an off-label medication for hospitalized COVID-19 patients weighing 50kg or more.[1]

Research Questions:

1. What is the safety profile of hydroxychloroquine sulfate compared to common outpatient medications such as acetaminophen and ibuprofen in terms of major and minor adverse effects?
2. Could hydroxychloroquine sulfate be used as an outpatient medication to treat COVID-19?

METHOD

Three independent investigators searched available online sources for the safety profile of each drug, compared, and contrasted reported major and minor adverse events. Disagreement was settled by discussion and consensus among three investigators. When agreement could not be reached, final selection was made from the primary investigator.

RESULTS

Hydroxychloroquine sulfate has a relatively safe profile with no major adverse events (no death or hospitalization) compared to acetaminophen and ibuprofen. In addition, hydroxychloroquine sulfate has similar rates of potential minor adverse events (gastrointestinal,

dermatologic, ophthalmologic, and cardiac side effects) compared to acetaminophen and ibuprofen.

CONCLUSION

Overall, we found that hydroxychloroquine sulfate has a relatively safe short-term use profile when compared to acetaminophen and ibuprofen on available databases. We believe hydroxychloroquine sulfate is reasonably safe to use in outpatient for indicated COVID-19 patients who have no pre-existing cardiac arrythmias and no contraindications to the medication.

INTRODUCTION

Hydroxychloroquine sulfate was originally used to prevent and treat malaria in the 1950s. Currently, hydroxychloroquine sulfate is approved to treat autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus. Molecular research has shown hydroxychloroquine sulfate has lyposomotropic, anti-inflammatory, and immunomodulatory mechanisms.[2] Despite being on the market for over 60 years, there are no clinical trials evaluating the safety profile of hydroxychloroquine sulfate in comparison to common medications used to manage non-acute symptomatic COVID-19 patients such as acetaminophen or ibuprofen.

Acetaminophen was first approved by the U.S. Food and Drug Administration in 1951 and became a popular drug in the 1980s when it became generic.[3] Currently, it remains one of the most prescribed medications in the United States, ranking as the 25th most prescribed drug in 2017 with 24,742,095 prescriptions.[4] Other names of acetaminophen are Tylenol, Paracetamol and MAPAP. This drug is available over the counter and is commonly used as an analgesic and antipyretic.

Ibuprofen is another medication being used in the treatment of COVID-19 symptoms. This drug has anti-inflammatory properties along with its analgesic and antipyretic properties. Ibuprofen is also a very commonly prescribed drug in the U.S. and ranks at 28th place with 24,070,989 prescriptions.[4] Other names of ibuprofen are Advil, NeoProfen, and I-Prin. This medication is also available over the counter and is commonly used for common cold symptoms as an analgesic and antipyretic.

Due to the widespread media attention on hydroxychloroquine sulfate as a possible treatment of COVID-19, the members of the general public may seek to take hydroxychloroquine sulfate or "sound-similar chloroquine medication" to self-medicate, as they would with acetaminophen or ibuprofen.

However, the use of hydroxychloroquine sulfate without the supervision of a healthcare professional can be dangerous. In March 2020, an Arizona man died after ingesting a form of chloroquine phosphate used to treat aquariums in an attempt to self-medicate for the novel coronavirus.[5]

In terms of used frequency, hydroxychloroquine sulfate is prescribed at a lower amount than either acetaminophen or ibuprofen. However, hydroxychloroquine is still a popular medication. It was the 128th most prescribed drug in the U.S. in 2017 at 5,666,999 prescriptions.[4]

The general public and some healthcare professionals may not have a thorough understanding of the indication and safety of hydroxychloroquine sulfate as a medication. Our goal in this paper is to provide a better understanding of hydroxychloroquine sulfate's safety profile for the general public and dispel any misconceptions that may exist.

METHODS

We conducted a search using various internet resources during March and April 2020 for safety data on the three medications from 2000 to 2020. Hydroxychloroquine sulfate, acetaminophen, and ibuprofen basic pharmacokinetics and pharmacology were extracted from FDA and their respective manufacturers. Three authors independently extracted the data. Disagreement was settled by discussion and consensus among three investigators. When agreement could not be reached, final selection was made from the primary investigator.

The final search was made in April 2020. Searches were made on MEDLINE (PubMed), Drug Watch, the Cochrane Central Register of Controlled Trials (CENTRAL), Package Insert, Micromedex, LexiComp, and Center of Drug Evaluation and Research for studies released through April 2020. Keywords were selected to include hydroxychloroquine-related, common cold-related, ibuprofen-related, acetaminophen-related, and randomized controlled trial-related words.

RESULTS

Based on the available search database, we are able to compare and contrast key features of the three drugs. Tables 1 describe basic information about each drug while Table 2 gives findings of major adverse events and Table 3 gives findings of minor adverse events.

Table 1: General Information on HCQ, Acetaminophen, and Ibuprofen. [6-8]

	Hydroxychloroquine Sulfate[6]	**Acetaminophen[7]**	**Ibuprofen[8]**
FDA Approved Indications	Anti-malarial, Rheumatoid Arthritis, Systemic Lupus Erythematosus	Analgesic, antipyretic.	Analgesic, antipyretic, dysmenorrhea, gout, osteoarthritis, rheumatoid arthritis
Recommended Dosage	200mg daily, Max 600 mg/daily	325 mg to 650mg every 4 to 6 hours, Max 4g/daily	200 to 800 mg three to four times a day, Max 3.2 g/day
Mechanism of Action (MOA)	Weak base - may work by concentrating the acid vesicles of parasites and inhibiting polymerization of heme. Anti-inflammatory mechanism unknown.	Analgesic MOA not fully known, believed to be via activation of descending serotonergic inhibitory pathways in CNS; antipyretic effect via inhibition of the hypothalamic heat-regulating center	Inhibition of cyclo-oxygenase (COX-1 and COX-2) and prostaglandin (PG) pathways.
Metabolism	Liver partially (CYP450)	Liver (CYP450-mainly via 3A4)	Liver (CYP450 via 2C8, CYP2C9)
Excretion	urine, bile	urine	Urine, feces
Contraindications	Hypersensitivity to 4-aminoquinoline compounds, retinal or visual field changes	Hypersensitivity to drug/class/components, severe hepatic impairment, severe active liver disease	Hypersensitivity to drug/class/components, ASA or NSAID-induced asthma or urticaria, aspirin triad, pregnancy starting at 30 wk gestation, CABG surgery perioperative use
1/2 Life	32-50 days	2-3 hours (adults)	1.8-2 hours (oral)
Common AEs	Dizziness, ataxia, headache, abdominal pain, nausea, vomiting, diarrhea, pruritus, weight loss, hair bleaching, photosensitivity, tinnitus, vision changes	Nausea, vomiting, and headache	Dyspepsia, nausea, abdominal pain, constipation, headache, dizziness, rash, liver function test (LFT) elevation, fluid retention, tinnitus, ecchymosis, photosensitivity, delayed ovulation

Table 2: Major Adverse Events on HCQ, Acetaminophen, and Ibuprofen according to 2018 Annual Report of American Association of Poison Control Center National Poison Data System.[9]

	Hydroxychloroquine	**Acetaminophen**	**Ibuprofen**
# of Case Mentions	None reported	43,318	80,850
Cases requiring hospitalizations	None reported	17,489	14,733
Cases resulting in Major Outcome	None reported	786	74
Cases resulting in Death Outcome	None reported	82	1

Table 3: Minor Adverse Drug Reactions (ADRs) of HCQ, Acetaminophen, and Ibuprofen[10-12]

Adverse Side Effects	**Hydroxychloroquine [7,10]**	**Acetaminophen[11]**	**Ibuprofen[12]**
Gastrointestinal	≥10% (abd pain and nausea) 1-10% (diarrhea and vomiting)	34% (nausea) 15% (vomiting) ≥5% (constipation) 1-5% (diarrhea and abd pain)	1-10%
Hepatic	0.01%-1% (increased liver enzymes)	1-5% (increased liver enzymes) 1-3% (increased AST/ALT)	1-10% (elevated liver enzymes) ≤ 15% (increased AST/ALT) <1% (hepatic failure/necrosis)
Ophthalmic	1-10% retinopathy	1-5% (periorbital edema)	<1%
Dermatologic	1-10% (rash and pruritus) Not known (SJS)	1-3% (pruritus) ≥ 5% (rash) Not known SJS	1-10% (rash and pruritus) <1% (SJS)
Cardiovascular	Possible QT prolongation unknown incidence	1-3%	1-10% (CV edema) <1% (other CV ADRs)

CONCLUSION

In our review, we looked at data from the U.S. National Poison Data System and extracted the data for cases involving hydroxychloroquine sulfate, acetaminophen, and ibuprofen exclusively from 2018. The data revealed that there were no reported cases of hydroxychloroquine sulfate causing major side effects that lead to hospitalizations or deaths in 2018. Meanwhile, in the same year, there were 17,489 cases and 14,733 cases requiring hospitalization for acetaminophen and ibuprofen, respectively. Out of these hospitalized cases, 82 cases and 1 case resulted in death for acetaminophen and ibuprofen respectively.[9]

Furthermore, data was extracted from multiple randomized control trials (RCTs) for the common adverse drug reactions (ADRs) of each of the three medications. All three medications had significant gastrointestinal side effects, including nausea, vomiting, abdominal pain, diarrhea and constipation. Rates of dermatologic reactions, including skin rash and pruritus, were comparable between the three medications, all between 1-10%. Notably, ibuprofen appears to have the highest rate of hepatic ADRs out of all three. These reactions include increased liver enzymes, elevated AST and ALT, and hepatic failure/necrosis. However, it is important to note that acetaminophen accounts for more than 50% overdose-related acute liver failure and about 20% of liver transplant cases in the United States.[13] At recommended doses, acetaminophen appears to be safe for the liver, however, overdoses of this medication can pose significant harm to the hepatic system. Lastly, ibuprofen had the highest incidence of cardiovascular adverse reactions, most significant for cardiovascular edema.

Hydroxychloroquine sulfate had the most significant rate of ophthalmic ADRs of the three medication. One of the most serious reactions observed being retinal toxicity, which is seen after prolonged use, usually after 5 years of continuous use.[14] Therefore, long-term use of

hydroxychloroquine sulfate requires frequent careful ophthalmic monitoring. While cardiac adverse effects are not common with hydroxychloroquine sulfate, some studies have linked the medication to QT interval prolongation. Ventricular arrhythmias and torsade de pointes have been reported in patients taking this medication.[6] Therefore, hydroxychloroquine sulfate should not be taken with other medications that have potential to prolong QT interval. Although no major cardiovascular incident has been reported, clinical signs and symptoms of arrhythmias and cardiomyopathy should also be monitored in patients taking hydroxychloroquine sulfate.

In conclusion, all three medications were shown to be relatively safe in short-term use. The use of hydroxychloroquine sulfate is still experimental in the treatment of COVID-19 in hospitalized patients. Our literature review suggests that hydroxychloroquine sulfate can be a safe medication for COVID-19 in an outpatient setting if hydroxychloroquine has a proven therapeutic intervention in hospitalized patients and the medication is prescribed and monitored by a healthcare professional. Emphasis should be placed on ophthalmic and cardiac monitoring. The efficacy and safety of hydroxychloroquine sulfate in COVID-19 patients need to be explored further with larger and longer RCTs. Further studies will contribute to our understanding of these three medications and what role they can play in the treatment of COVID-19.

DISCUSSION

When considering the results of this review, we acknowledge several limitations and confounding factors may weaken this study. First, there were no head-to-head randomized clinical trials comparing the safety profiles of hydroxychloroquine sulfate, acetaminophen, and ibuprofen. Patients who were taking combinations of both acetaminophen and ibuprofen were not accounted for in the safety analysis. Hydroxychloroquine sulfate is prescription only, typically used in a different subtype patient population (malaria, systemic erythematous lupus

and rheumatoid arthritis) than those taking ibuprofen and acetaminophen and therefore, these patients are being monitored carefully. On the other hand, acetaminophen and ibuprofen are over-the-counter medications, and patients are less likely to be monitored by a healthcare professional while taking these medications. In addition, due to the ubiquitous nature of acetaminophen and ibuprofen as over-the-counter analgesics and antipyretics, these medications are being used by a much larger patient population and at a higher rate.

On April 7, 2020, FDA issued safety alert surrounding use of hydroxychloroquine for approved indication of the aforementioned three treatment conditions. Side effects mentioned in this alert include irreversible retinal damage, cardiac effects (including cardiomyopathy and QT prolongation), worsening of psoriasis, and hypoglycemia. The warning did not include short term treatment in the unlabeled use in COVID-19 patients.[15]

In conclusion, the available data suggests that hydroxychloroquine sulfate has a good short-term safety profile when compared to acetaminophen and ibuprofen. Based on the available research, hydroxychloroquine sulfate is reasonably safe to use in COVID-19 patients. More controlled randomized clinical trials are needed to support the safety and efficacy of hydroxychloroquine sulfate in those affected with this novel coronavirus. Further research will also allow for exploration of optimal treatment dosage and duration.

Key Words: COVID-19, hydroxychloroquine sulfate, HCQ, acetaminophen, ibuprofen, side effects, drug safety, Meta-analysis

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