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Original Research Article

A decade of experience in prescribing hydroxychloroquine and azithromycin: A retrospective analysis of medication queries in a Saudi drug and poison information center

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Abstract

Purpose: *To analyze drug information queries related to treatment with hydroxychloroquine (HCQ), chloroquine (CQ), and azithromycin submitted to a local drug and poison information center in Riyadh, Saudi Arabia.*
Methods: *This retrospective study explored HCQ-, CQ-, and azithromycin-related inquiries submitted to the Drug and Poison Information Center at the Security Forces Hospital Program, Riyadh, Saudi Arabia. These inquiries were analyzed quantitatively and qualitatively. The quantitative analysis included the frequency of each request per year, the profession of the requesters, and the source material classification. A thematic analysis was also performed to categorize requests from healthcare professionals.*
Results: *The Drug and Poison Information Center received 10,685 usable inquiries between 2005 and 2018. There were 160 CQ-, HCQ-, and azithromycin-related queries. Most requests were made by pharmacists (61.25 %). The main sources used to answer the queries were tertiary (92.31 %) and primary (7.69 %) sources. In the dataset, three major topics were identified: administration and dosing, safety, and pregnancy and lactation, each associated with a query subset.*
Conclusion: *These results emphasize the importance of continued education on antimicrobial agents in general, and HCQ, CQ, and azithromycin in particular. The three items have been identified as focus areas that policymakers can us to ensure the quality of future medication prescriptions.*

Keywords: *Hydroxychloroquine, Chloroquine, Azithromycin, COVID-19 treatment, Drug information queries, Antimicrobial agent*

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INTRODUCTION

The outbreak of the coronavirus disease 2019 (COVID-19) originated in Wuhan, China, from where it quickly spread globally [1]. Most patients with COVID-19 are either asymptomatic or present with mild symptoms including fever, cough, and fatigue. In some patients, however, it causes progressive respiratory failure and massive alveolar damage that can be fatal,

especially in people with underlying conditions, elderly patients, and immunocompromised patients [1]. To date, there is no specific treatment for COVID-19, but medications initially developed to treat other viral infections are now being tested for efficacy against SARS-CoV-2, the virus that causes COVID-19 [1]. Several studies have found that hydroxychloroquine (HCQ) and chloroquine (CQ) inhibit angiotensin-converting enzyme-2 glycosylation and significantly reduce the infection of host cells by SARS-CoV-2 *in vitro* [2]. Moreover, the results of a study by Gautret *et al* suggested that the combination of HCQ and azithromycin exerts a synergistic effect [3].

Both CQ and HCQ have been approved by the US Food and Drug Administration (FDA) for the prevention and treatment of malaria [4]. HCQ has also been approved by the US FDA for use in systemic lupus erythematosus and rheumatoid arthritis [4]. Both medications have excellent oral absorption and bioavailability with a long half-life, which only requires infrequent dosing to prevent and treat malaria [4]. Moreover, both treatments are reportedly inexpensive, widely available, safe, and their side effects are commonly mild and transient [4].

Azithromycin acts as a broad-spectrum antibiotic with bacteriostatic activity and forms part of a subclass of macrolide antibiotics known as azalides. Its activity spectrum includes the *Mycobacterium avium* complex, *Treponema pallidum, Mycoplasma pneumoniae*, and *Chlamydia* species [5]. Azithromycin is effective against the Zika and Ebola viruses *in vitro* [6], and prevents serious respiratory tract infections when administered to patients suffering from viral infections [5].

The role of drug information centers in healthcare settings has increased greatly due to the high influx of pharmaceutical molecules that pose serious challenges to healthcare professionals. Pharmacists play a critical role in promoting appropriate drug use by providing reliable and useful information on drugs, ultimately leading to better patient outcomes. Drug information request electronic forms are commonly used to document drug queries from healthcare professionals [7]. These queries can also be used to identify areas of limited knowledge among healthcare professionals.

The objective of this study was to analyze drug information queries related to HCQ, CQ, and azithromycin treatments that were submitted to a local drug and poison information center (DPIC) between 2005 and 2018 and provide updated information regarding these queries.

METHODS

This retrospective study included all inquiries submitted between January 1, 2005 and December 31, 2018 to the Drug & Poison Information Center (DPIC) at the Security Forces Hospital Program, Riyadh, Saudi Arabia, which is a tertiary care facility with over 500 beds that delivers healthcare to the Ministry of Interior employees and their families. Institutional Review Board (IRB) approval was obtained from the research committee of the Security Forces Hospital Program (approval no. 19-357-55).

All inquiries received at the DPIC which mentioned HCQ, CQ, and azithromycin were assessed for brand names associated with each treatment. Local brand names were examined using the Saudi Food and Drug Authority website, specifically the portal for drugs registered in Saudi Arabia. International brand names were verified using Drugdex [8].

Each inquiry was analyzed quantitatively and qualitatively. The quantitative analysis included the frequency of each request year, profession of the requester, and classification of the assessed reference. The request years were divided into two periods: 2005–2012 and 2013–2018. The cutoff year 2013 was chosen due to the inauguration of a nationwide DPIC that serves all healthcare institutions and the public [9]. The references were classified as either primary or tertiary sources. Primary sources included the most recent information available, such as randomized clinical trials and other journal articles, except for review articles [10]. Tertiary sources were all types of materials that summarized or condensed the primary materials. Tertiary sources included books, pharmacy electronic databases, review articles, and compendia [10]. The type of profession providing the answers was classified as a pharmacist versus other healthcare professionals. Statistical analyses were performed using the R Studio-Integrated Development Environment software.

Data analysis

The inquiries were qualitatively analyzed using a thematic analysis method. This method was defined as a technique focused on the interpretation of qualitative information patterns that should be identified and analyzed by researchers [11]. As part of the analysis process, two researchers independently coded the topics of each inquiry. Ultimately, these topics were

classified as: therapeutics and safety, identification, administration and dosage, availability and supply, side effects and interactions, and pregnancy and lactation. Inquiries pertaining to topical use were excluded from the analysis due to their incompatibility with the study objective.

RESULTS

The assessment of the inquiries submitted to the DPIC between 2005 and 2018 identified 10,685 usable queries (Figure 1). Further screening identified 160 inquiries related to CQ or HCQ (15 %) and azithromycin (85 %). Approximately 60 % of these inquiries were received before 2010 (85 questions), and 40% were received during or after 2013 (58 questions). Most queries were submitted by pharmacists, who accounted for 61.25 % of the inquiries received by the DPIC, whereas 38.75 % contributed by other healthcare professionals; 34.27 % physicians, and 4.48 % nurses. Moreover, the majority of queries were asked by healthcare professionals associated with the hospital. Tertiary sources were used to address 92.31 % of the questions, and primary sources were consulted to answer the remaining questions (7.69 %). The main tertiary source of information was Drugdex (85.61 %).

Three major categories, each associated with a subset of queries, were derived from the dataset (Table 1). One category focused on the aspects of pregnancy (7.7 %) and lactation (1.41 %) when using any of the studied medications. The administration and dosage category represented an essential part of the queries (50 %), which covered a range of topics related to specific diseases such as pneumonia or systemic lupus

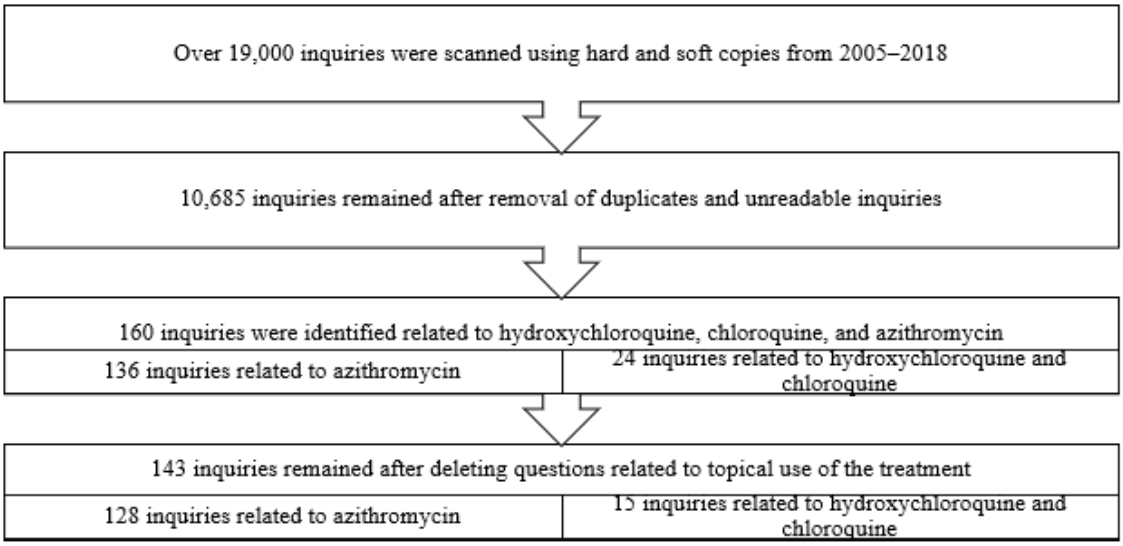

Figure 1: Flowchart of extracting inquiries related to hydroxychloroquine, chloroquine, and azithromycin

Table 1: Samples of drug-related inquiries submitted to the DPIC between 2005 and 2018

Question	Category
• *"Can **hydroxychloroquine** be given to a **pregnant** female?"*	Pregnancy
• *"Can **hydroxychloroquine** be given 200 **mg** bid?"*	Administration & Dosage
• *"Can we prescribe **azithromycin** for 6 days in pneumonia?"*	Administration & Dosage
• *"Does cyclosporine or **azithromycin** or doxycycline cause an increase in **triglycerides**?"*	Safety
• *"I have a **pregnant** patient; can I give her **azithromycin**?"*	Pregnancy
• *"Is it **safe** to administer carbimazole & **azithromycin**?"*	Safety
• *"What is the **dose** of **hydroxychloroquine** for systemic lupus erythematosus?"*	Administration & Dosage
• *"Would **hydroxychloroquine** 20 mg cause a **vision problem** or not?"*	Safety
• *"Can I **combine azithromycin** with cefuroxime for a patient with pneumonia?"*	Safety

erythematosus. Some queries in the administration and dosage categories covered issues related to the dosing of either HCQ or azithromycin. Several queries were assigned under the safety category: interaction (11.7 %), side effects (4.93 %), and overdose (2.11 %). The respective requests were focused on the two medications in relation to drug-drug interactions or drug-disease interactions.

Queries about azithromycin administration and dosing were mainly related to the dose for treating acne vulgaris and lower respiratory tract infections. Medication safety queries have focused on gastrointestinal side effects. Queries related to the safety of HCQ focused on vision problems.

DISCUSSION

This study analyzed drug information queries related to HCQ, CQ, and azithromycin, which resulted in an assessment of healthcare professionals' knowledge of the targeted treatment options. The quantitative analysis showed that the majority of the questions were answered using tertiary sources; thus, these questions can be classified as background information [10]. Indeed, HCQ and CQ have narrow indications, and it is expected that these treatments would be associated with limited knowledge from clinicians [4].

The results revealed that a higher proportion of requests were received before 2010. This could be attributed to two factors. First, HCQ was initially approved for malaria, and the number of cases has declined over the years [4]. Second, the Saudi Ministry of Health activated a unique national number that unified many public service tasks, including answering questions related to drugs and poisoning [9]. These two developments could explain the decreasing number of queries related to the assessed treatment options between 2005 and 2018.

Our qualitative analysis identified the major question topics that we assigned as administration and dosage, safety, and pregnancy and lactation. Queries about azithromycin administration and dosing were mainly related to the dose for treating acne vulgaris and lower respiratory tract infections. The adult dose for mild-to-moderate, community-acquired pneumonia is as follows: 500 mg tablet orally on the first day, then 250 mg each day from the second to the fifth day or one single dose of 2 g of extended-release suspension or 500 mg intravenously each day for a minimum of two days, then an oral dose of 500 mg each day until the end of the treatment course (7 to 10 days). For patients aged 6 months or older, the recommended first dose would be 10 mg/kg, but not exceeding 500 mg per dose orally either as a tablet or immediate-release suspension. The recommended second to the fifth day dose is 5 mg/kg but does not exceed 250 mg per dose; this dose is also recommended for outpatient treatment in children older than 3 months. For patients aged 6 months or older, who have a bodyweight of less than 34 kg, a single 60 mg/kg oral dose of extended-release suspension is recommended whereas for those with a body weight of 34 kg or more, a single 2 g oral dose for inpatient treatment is recommended. If older than 3 months, 10 mg/kg intravenously daily is recommended for at least 2 days, then increases by 5 mg/kg orally once daily to complete the treatment course. Azithromycin is not indicated for the treatment of *Acne vulgaris* [12].

The queries on administration and dosing of HCQ were mainly related to the dose for treating systemic lupus erythematosus. The adult dose for the treatment of lupus erythematosus is 200 – 400 mg orally once daily or equally divided twice daily, with a maximum dose of 400 mg/day. It is not recommended to treat lupus erythematosus in pediatric patients [12].

Medication safety queries were related to adverse effects and drug-drug interactions. The common adverse effects of azithromycin are injection site reaction, abdominal pain, diarrhea, flatulence, nausea, vomiting, increased liver enzymes, headache, and abnormal vision [12]. There are several contraindicated major and moderate drug-drug interactions, including those with cisapride, ergotamine, and sparfloxacin. Moreover, there are major interactions between warfarin and clarithromycin, as well as moderate interactions with atorvastatin in addition to many other interactions [26]. Benn *et al.* reported that headaches, gastrointestinal upset, and dizziness are common adverse effects of azithromycin. In addition, malignant arrhythmias and prolongation of the rate-corrected electrocardiographic QT (QTc) interval have been reported [13].

HCQ has been associted with several serious adverse effects, such as torsade de pointes, hypoglycemia, agranulocytosis, aplastic anemia, thrombocytopenia, muscle disorders, retinal disorders, hearing loss, and angioedema. Approximately 7.5% of the patients had retinal disorders [12]. The major risk factors for HCQ are its interactions with many other drugs. HCQ co-administration with most of these drugs is contraindicated, including cisapride and sparfloxacin, as well as amiodarone and

moxifloxacin. Shipman *et al.* stated that the use of HCQ for cutaneous lupus erythematosus is effective at a dose of 400 mg/day, with an extremely low incidence of adverse effects, such as retinopathy [14].

Both azithromycin and HCQ have a known risk of QTc prolongation leading to torsade de pointes with an approximate rate of 200 – 250 bpm and an irregular rhythm without Py wave and PR interval. Since the new regimen recommends using the HCQ-azithromycin combination for COVID-19 treatment, the risk score for predicting QTc interval prolongation should be performed for the patient before treatment initiation. Moreover, it will be essential during treatment to perform EKG monitoring, avoid any other medication that could affect QTc, and correct potential electrolyte imbalance [12].

Fetal risk cannot be ruled out when using azithromycin during pregnancy and lactation. The U.S. FDA pregnancy category B indicates that they lack strong evidence in pregnant women, and animal studies have failed to demonstrate a risk to the fetus [12]. Furthermore, there is a potential risk for infants during lactation [12]. Specifically, azithromycin is secreted into human milk and should be used only if needed. According to Sarkar *et al.*, pregnant women exposed to azithromycin did not show an increase in the incidence of major malformations above the baseline of 1% – 3%, and macrolide antibiotics are generally safe during pregnancy [15].

For the use of HCQ in pregnancy and lactation, Australia's Therapeutic Goods Administration has assigned pregnancy category D, but there is no assigned U.S. FDA pregnancy category. Thus, the use of HCQ should be avoided during pregnancy, except for malaria therapy. This drug passes through the placenta, however, infant risk is minimal [12]. Numerous studies have shown that patients with lupus erythematosus, who continued HCQ during pregnancy, had diminished flares and improved pregnancy outcomes, including longer fetal gestation and higher birth weight of infants [16]. Encouragingly, Flint *et al* reported that antimalarial drugs are compatible with pregnancy, without any sign of safety alarms, and that several professional society guidelines recommend continuing HCQ during pregnancy [17]. Moreover, in support of this approach, a survey among North American rheumatologists showed that more than 69% of the rheumatologists continued providing HCQ prescriptions for their pregnant patients [18].

Limitations of the study

This study highlights areas where continuous education is needed with regard to therapeutic treatments. However, it is important to emphasize that the purpose of this study was not to reach conclusions regarding the appropriateness of using HCQ, CQ, and azithromycin for patients with COVID-19. The strongest evidence of clinical information can be obtained from meta-analyses and randomized clinical trials [10]. Moreover, the information obtained in this study was based on a single center, and future research could validate similar methodologies in different centers.

CONCLUSION

Findings from this retrospective study emphasize the importance of continued education about antimicrobial agents in general, and specifically about HCQ, CQ, and azithromycin. The three items can be used by policymakers as focus areas to ensure the quality of future medication prescriptions.

DECLARATIONS

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Conflicts of interest

No conflict of interest is associated with this work.

Contribution of authors

The authors declare that this study was done by the authors named in this article and that all liabilities pertaining to claims relating to the content of this article will be borne by them. Althemery supervised the work, designed the conceptual framework, took part in the methodology, and funds allocation. Alnajjar was responsible for data curation and methodology. Almalki worked on data acquisition and investigation. Alfaifi validated the methodological process and participated in writing the manuscript. Nehad contributed to writing, reviewing, and editing of the manuscript. The manuscript was comprehensively read and approved for publication by all authors.

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