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Acute chloroquine and hydroxychloroquine toxicity: A review for emergency clinicians

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ABSTRACT

Background: Acute chloroquine and hydroxychloroquine toxicity is characterized by a combination of direct cardiovascular effects and electrolyte derangements with resultant dysrhythmias and is associated with significant morbidity and mortality.
Objective: This review describes acute chloroquine and hydroxychloroquine toxicity, outlines the complex pathophysiologic derangements, and addresses the emergency department (ED) management of this patient population.
Discussion: Chloroquine and hydroxychloroquine are aminoquinoline derivatives widely used in the treatment of rheumatologic diseases including systemic lupus erythematosus and rheumatoid arthritis as well as for malaria prophylaxis. In early 2020, anecdotal reports and preliminary data suggested utility of hydroxychloroquine in attenuating viral loads and symptoms in patients with SARS-CoV-2 infection. Aminoquinoline drugs pose unique and significant toxicological risks, both during their intended use as well as in unsupervised settings by laypersons. The therapeutic range for chloroquine is narrow. Acute severe toxicity is associated with 10–30% mortality owing to a combination of direct cardiovascular effects and electrolyte derangements with resultant dysrhythmias. Treatment in the ED is focused on decontamination, stabilization of cardiac dysrhythmias, hemodynamic support, electrolyte correction, and seizure prevention.
Conclusions: An understanding of the pathophysiology of acute chloroquine and hydroxychloroquine toxicity and available emergency treatments can assist emergency clinicians in reducing the immediate morbidity and mortality associated with this disease.

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1. Introduction

Chloroquine and hydroxychloroquine are aminoquinoline derivatives widely used in the treatment of rheumatologic diseases as well as for malaria prophylaxis [1]. In early 2020, anecdotal reports and preliminary data suggested utility of chloroquine and hydroxychloroquine for attenuating viral loads and symptoms in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2-5]. Clinical trials are underway to determine treatment protocols, efficacy, and optimal dosing for SARS-CoV-2 infection [6]. Shortly following publication of initial reports indicating efficacy, cases of acute chloroquine toxicity including inadvertent deaths were reported in the United States (U.S.), African, and European newsmedia [7-9]. There were 283 chloroquine and hydroxychloroquine exposures reported to U.S. Poison Control Centers from January 1, 2020 through April 26, 2020, an increase of 42% compared to the same time period during the previous year, with a 93% increase during the month of April 2020 when compared to April 2019 [10]. Aminoquinoline drugs, including chloroquine, hydroxychloroquine, and amodiaquine, pose unique and significant toxicological risks, both in therapeutic use as well as in unsupervised settings by laypersons. For the purposes of this review, "aminoquinolines" will refer to chloroquine and hydroxychloroquine.

The therapeutic margin for chloroquine toxicity is narrow, and acute severe toxicity is associated with 10–30% mortality owing to a combination of direct cardiovascular effects and electrolyte derangements with resultant dysrhythmias [11]. In typical use, aminoquinoline toxicity is rarely reported. Fewer than 10 cases of acute severe chloroquine or hydroxychloroquine overdoses were reported to U.S. Poison Control Centers from 2012 to 2018, and approximately 70 cases of chloroquine or hydroxychloroquine overdose were reported in the literature base in

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the past decade [12-18]. While commonly prescribed for rheumatologic diseases, the novel proposed indication for SARS-CoV-2 infection represents an unprecedented expansion of aminoquinoline use in a significantly wider population [6].

As acute aminoquinoline toxicity is rare, contemporary literature on management is sparse [19]. Similar to other toxicological emergencies, randomized controlled trials and systematic reviews analyzing management approaches are absent. Prospective clinical trials evaluating treatment are also rare and date back to the 1980s and 1990s [20,21]. Updated treatment recommendations for aminoquinoline toxicity since the development of rescue modalities including intravenous lipid emulsion (ILE) and extracorporeal membrane oxygenation (ECMO) are lacking [22]. This article reviews the pathophysiology of aminoquinoline toxicity to provide guiding principles for management of acute complications. Understanding these complications and the approach to the management of electrolyte imbalances and hemodynamic instability is essential to optimizing patient care, especially following acute intoxication that may bring patients to the emergency department.

2. Methods

This review provides a focused evaluation of emergency department-based evaluation and treatment of aminoquinoline toxicity. The authors searched PubMed and Google Scholar for articles containing the key words “hydroxychloroquine” OR “aminoquinoline” OR “chloroquine” OR “quinolone” AND “toxicity” OR “poisoning” OR “adverse effects”. The PubMed search was conducted from database inception to April 5, 2020, yielding over 6300 articles. The first 200 articles in Google Scholar were also evaluated for inclusion. The literature search was restricted to studies published in English, with a focus on emergency medicine and critical care. Authors evaluated case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. Articles were chosen based upon author consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews, when alternate data were not available. A total of 121 articles were selected for inclusion in this narrative review.

3. Discussion

3.1. Proposed aminoquinoline uses in coronavirus infection

Chloroquine and hydroxychloroquine are derivatives of quinine, derived from the bark of the Peruvian Cinchona tree. Chloroquine was synthesized in 1934 but shelved for years due to concerns for toxicity in human patients. Hydroxychloroquine sulfate was developed in 1946 in an effort to produce a less toxic chloroquine analog. Animal toxicological studies demonstrate hydroxychloroquine to be approximately 40% less toxic than chloroquine [23]. Initially indicated for antimalarial treatment and prophylaxis, chloroquine and analogs found new anti-inflammatory use in World War II. As millions of soldiers used it against malaria, military physicians observed improvement in inflammatory arthritis, leading to trials demonstrating aminoquinoline efficacy for rheumatologic conditions [24]. Antimalarial efficacy of chloroquine waned in the late 20th century, though it is still used for malarial prophylaxis in regions with susceptible *Plasmodium* strains. Chloroquine analogues have also been found to have metabolic, antithrombotic, antineoplastic, and antiviral effects, and have been hypothesized as targeted agents against coronavirus infection since the 2003 SARS outbreak [25,26].

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is responsible for a major international pandemic with significant morbidity and mortality rates between 1.5 and 9% depending on the population investigated [27,28]. The pathophysiology of SARS-CoV-2 includes but is not limited to cytokine dysregulation, direct cytopathic effects on respiratory tract epitheliocytes, and down-regulation of lung protective angiotensin converting enzyme resulting in diffuse alveolar damage and hypercoagulability [29,30]. Viral entry is facilitated by cellular protease-primed spike protein binding to angiotensin-converting enzyme 2 (ACE2) receptors [31]. Efforts to repurpose or develop targeted therapeutics for SARS-CoV-2 infection have included assessment of anti-inflammatory drugs such as corticosteroids and interleukin inhibitors, macrolide antibiotics such as azithromycin, and direct-acting antivirals such as protease inhibitors and adenosine analogs [6]. The utility of aminoquinolines in attenuating infection severity is hypothesized to derive from preventing SARS-CoV-2 binding to target receptors and inhibiting viral cell entry [6]. Chloroquine and hydroxychloroquine are concentrated within the endosome, where they are thought to modulate organelle pH, inhibiting autophagosome formation and impairing cleavage of the SARS-CoV-2 spike protein [32]. Additional hypothesized immunomodulatory effects in SARS-CoV-2 infection include downregulation of T-cell response and inflammatory cytokine storm that play a role in organ injury and acute respiratory distress syndrome [32,33]. Preliminary in-vitro data and clinical trials in China and France in early 2020 using chloroquine and hydroxychloroquine suggested anti-SARS-CoV-2 activity [2,34]. These clinical trials utilized chloroquine at dosages and treatment courses greater than those prescribed for antimalarial and rheumatologic indications, raising concern for toxicological implications in susceptible patients. Following the United States Food and Drug Administration emergency use authorization for chloroquine and hydroxychloroquine in the treatment of SARS-CoV-2, many additional clinical trials with randomization, blinding, and larger sample sizes were initiated to determine the benefit and risks. The largest of these studies, enrolling over 96,000 patients, initially demonstrated increased in-hospital mortality rates in patients treated with chloroquine or hydroxychloroquine [35]. However, that study has since been retracted due to concerns regarding veracity of the data and analyses conducted and inability to conduct an independent and private peer review [36]. Additional studies have demonstrated similar findings of increased mortality or did not find any evidence of prevention of primary endpoints, such as need for mechanical ventilation or death in patients treated with aminoquinolines [37-39]. As of June 2020, there are over 40 ongoing clinical trials actively assessing the efficacy of chloroquine or hydroxychloroquine, demonstrating continued interest in its role as a therapeutic agent for COVID-19. Furthermore, additional trials targeting frontline healthcare workers are underway to assess for the possible preventative action of these agents. The use of chloroquine or hydroxychloroquine sulfate in combination with other novel antiviral agents has been discouraged by the United States Food and Drug Administration, as recent in-vitro data demonstrating increasing concentrations of chloroquine phosphate reduced formation of activated remdesivir triphosphate in human bronchial epithelial cells, raising concerns that it may reduce the antiviral activity of this medication [40]. Widespread non-prescription use of aminoquinolines for either prophylaxis or treatment by laypersons in response to fears of COVID-19 raises significant and continued concern for unintended toxicity from overdose and/or drug-drug interactions.

3.2. Chloroquine and hydroxychloroquine toxicology

3.2.1. Metabolism and pharmacokinetics

Despite slight differences in chemical structure, chloroquine and hydroxychloroquine are similar in regard to both metabolism and toxicity [41,42]. Both molecules are highly lipophilic, have a high volume of distribution, and have mild-to-moderate protein binding [43,44]. Following ingestion, the drugs are rapidly absorbed from the upper gastrointestinal (GI) tract and slowly redistribute to other compartments, eventually accumulating in erythrocytes, liver, lung, kidney, heart, muscle, and retinal tissue [43]. The combination of rapid absorption, high