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RESEARCH LETTER

Hydroxychloroquine and Chloroquine Toxicity as Reported by Medical Toxicologists to the Toxicology Investigators Consortium (ToxIC) Registry

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Introduction

Chloroquine and hydroxychloroquine, 4-aminoquinoline drugs, have long-standing use as antimalarials and in inflammatory conditions. Early investigations in pharmacotherapy to treat Coronavirus Disease 2019 (COVID-19) infections focused on hydroxychloroquine as a promising candidate [1–3]. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) on March 28, 2020, for the treatment of COVID-19 with chloroquine and hydroxychloroquine in the context of clinical trials [4]. Later investigations demonstrated increased morbidity and mortality, largely owing to cardiotoxicity associated with hydroxychloroquine [5]. The FDA retracted its EUA on June 15, 2020, warning not to use these agents to treat COVID-19 [6].

According to the FDA Adverse Effects Reporting System, in the first 7 months of 2020 there were 20 reports of death where hydroxychloroquine was listed as the primary agent in individuals using it as an unapproved COVID-19 treatment [7]. In order to better define the toxic profile of individuals who may experience poisoning by hydroxychloroquine and the related drug chloroquine, we utilized the Toxicology Investigators Consortium (ToxIC) Case Registry to describe the largest case series to date that includes clinical presentations and treatments recorded prior to the COVID-19 pandemic. We describe available information from the Registry on critical illness, including information on hemodynamic instability, central nervous system (CNS) depression, seizures, and death as well as intention of exposure.

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Methods

The ToxIC Registry was established by the American College of Medical Toxicology in 2010 [8]. All cases entered into the Registry have been evaluated at the bedside by a board-eligible or board-certified medical toxicologist. There are currently > 50 participating facilities across the USA with additional sites in Canada, Israel, and Thailand [8]. The Registry has been reviewed by the Western Institutional Review Board (IRB) and operates in pursuant to the approval of the participating site IRBs.

Data were queried from the initiation of the Registry in January 2010 through 31 December 2019. Cases were included if they listed chloroquine or hydroxychloroquine as the agent of exposure in any primary agent field. Cases were excluded if they did not list chloroquine or hydroxychloroquine as a primary agent.

Demographic variables are presented descriptively, including intention of exposure if known. Continuous clinical variables including hemodynamics were presented as the mean (range). We reported frequency of therapies and antidotes reported in the registry. In cases where demographic information such as race was not recorded this was reported with the results.

Results

Demographics

Fifty-two cases met inclusion criteria: 48 involving hydroxychloroquine and 4 involving chloroquine. Available case demographics including gender, age range, and ethnicity are listed in Table 1.

Table 1 Demographics

Demographics—age and gender	
	N (%)
Gender	
Female	41 (78.8)
Male	11 (21.2)
Pregnant	1 (1.9)
Age range (years)	
< 2	3 (5.8)
2–18	17 (32.7)
19–65	27 (51.9)
66–89	5 (9.6)
Total	52 (100)
Demographics—race and Hispanic ethnicity	
	N (%)
Race	
Caucasian	14 (26.9)
Black/African	8 (15.4)
Unknown	7 (13.5)
Mixed	2 (3.8)
Asian	1 (1.9)
Other	1 (1.9)
Not reported	19 (36.5)
Total	52 (100)
Hispanic Ethnicity	
Hispanic	5 (9.6)
Non-Hispanic	24 (46.2)
Unknown	4 (7.7)
Not reported	19 (36.5)
Total	52 (100)

Clinical signs, treatments and interventions

The most common clinical symptoms were hypotension with a systolic blood pressure < 80 mmHg (32.7%), QTc prolongation > 500 ms (msec) (26.9%) with a median reported of 510.6 ms (range 309—789 ms), and CNS depression (38.5%). Further clinical features and a complete list of treatments performed are listed in Table 2.

Intentional Ingestions

Thirty-seven of the 52 cases (71.2%) involved intentional ingestions and 22 (59.5%) of them were attempts at self-harm. The other cases reflected therapeutic intent. There was one death reported (1.9%), with life support being withdrawn in that case. About half of patients with an intentional ingestion (48.6%) required intensive care admission. Fifteen cases reported hypotension (40.5%) and 13 (35.1%) reported QTc prolongation. Twenty (54.1%) experienced coma or central nervous system depression of which 10 (19.2%) required intubation or ventilatory management.

Unintentional Exposures

There were 12 cases (23.1%) of unintentional exposures, none of which required treatment interventions. Nine of these (75.0%) were age 6 or less. Only a single case of an 82-year-old man presenting for evaluation of an unintentional exposure reported delirium or toxic psychosis.

Coingestants

Acetaminophen was reported in 5 cases. Additional isolated coingestants included a variety of agents. When considered as agent classes, the most commonly reported were cardiovascular agents with 11 cases and analgesics with 10 cases.

Table 2 Clinical features

Clinical Features	
	N (%)
Vital Sign Abnormalities	
Hypotension (SBP < 80 mmHg)	17 (32.7)
Tachycardia (HR > 140 bpm)	4 (7.7)
Bradycardia (HR < 50 bpm)	3 (5.7)
Cardiac Toxicity	
QTC prolongation (> / = 500 ms)	14 (26.9)
QRS prolongation (> / = 120 ms)	6 (11.5)
Ventricular Dysrhythmia	3 (5.7)
Metabolic Abnormalities	
Metabolic Acidosis (pH < 7.2)	4 (7.7)
Elevated Anion Gap (> 20)	2 (3.8)
Neurologic Effects	
Coma/CNS Depression	20 (38.4)
Agitation	4 (7.7)
Delirium/Toxin Induced Psychosis	3 (5.7)
Seizure	3 (5.7)
Weakness/Paralysis	2 (3.8)
Hyperreflexia/Myoclonus/Clonus	1 (1.9)
Numbness/Paresthesia	1 (1.9)
Treatments and Interventions Provided	
	N (%)
Intravenous Fluid Resuscitation	16 (30.8)
Vasopressors*	14 (26.9)
Epinephrine	6 (11.5)
Norepinephrine	3 (5.8)
Dopamine	2 (3.8)
Phenylephrine	2 (3.8)
Vasopressin	2 (3.8)
Not recorded	3 (5.8)
Benzodiazepines	11 (21.2)
Intubation/Ventilator Management	10 (19.2)
Sodium Bicarbonate	10 (19.2)
Activated Charcoal	6 (11.5)
Lipid Rescue	3 (5.8)
N-Acetylcysteine	3 (5.8)
Cardiopulmonary Resuscitation	2 (3.8)
Gastric Lavage	2 (3.8)
Hemodialysis/Continuous Renal Replacement Therapy	2 (3.8)
Anticonvulsants	1 (1.9)
Atropine	1 (1.9)
Extracorporeal Membrane Oxygenation	1 (1.9)
Neuromuscular Blockers	1 (1.9)
Pacemaker placement	1 (1.9)
Therapeutic Hypothermia	1 (1.9)

* Vasopressors were used in 14 cases (26.9%), with 15 specific vasopressors recorded. Each case may have used more than one vasopressor agent so individual agents total more than fourteen. One patient had 3 vasopressors reported, and two patients had 2 vasopressors reported. Three cases did not record which vasopressor was used

SBP systolic blood pressure, *HR* heart rate, bpm beats per minute, QTC corrected QT, *CNS* central nervous system

**More than one clinical sign and symptom could be present in a single case, so the total sum is greater than 100%

*** Some Registry fields are created as a binary field definition. For example, tachycardia is defined as a heart rate > 140 beats per minute and is entered as a yes/no data point. Where relevant, these definitions are indicated

Antidepressants and sedative/hypnotic agents each were reported in 7 cases.

Discussion

Overdose events related to chloroquine/hydroxychloroquine have been reported related to COVID-19 [7, 9, 10]. Hydroxychloroquine remains an important and relatively commonly prescribed pharmaceutical used in the treatment of a variety of disorders. Our data demonstrate the clinical severity of hydroxychloroquine overdose cases managed by medical toxicologists and describe therapies that were used to manage these poisonings.

Poisoning from hydroxychloroquine most commonly manifested in this study with clinically significant hypotension, prolonged QTc, abnormal heart rate, and central nervous system depression. In this data set, there appeared to be a divergence in the severity of presentation between patients who presented with unintentional exposures as opposed to intentional ingestions. Specific laboratory values including potassium were not available for analysis. The clinical features that prompted intervention were more commonly seen in individuals who intentionally overdosed on hydroxychloroquine, most likely because they ingested a higher dose than those with unintentional exposures. Clinicians who evaluate individuals with an intentional overdose of hydroxychloroquine or chloroquine should closely monitor patients for signs of cardiotoxicity and neurotoxicity.

Traditional therapies recommended to manage hydroxychloroquine overdose include high dose diazepam, epinephrine and endotracheal intubation [11, 12]. In contrast to previously published recommendations on early intubation, our study found that few individuals ultimately required intubation, and most were successfully managed with benzodiazepines and other supportive measures. This may be reflective of the predominance of hydroxychloroquine in our study as opposed to chloroquine in previous studies [12]. However, the majority of individuals included in this study comprised intentional overdoses with suicidal intent. These larger ingestions were more likely to be symptomatic than the general population of all exposed patients or those taking therapeutic doses.

While epinephrine is the recommended vasopressor of choice, less than half of individuals who required vasopressor support received epinephrine. In this cohort the most common pharmacologic intervention among hydroxychloroquine poisoned individuals was benzodiazepines; however, which benzodiazepine used was not specified, so it is unknown whether diazepam was the preferred agent in this group.

Limitations

Limitations to this study include those inherent to a registry collection and have been previously described, including limited information on amount of xenobiotic ingested and lack of laboratory confirmation [13, 14]. Specific case details and laboratory values of interest may not be available. This registry relies on data entry from medical toxicologists who perform bedside evaluations; cases likely skew towards more symptomatic exposures who received a toxicology consultation, and therefore may not be generalizable to all ingestions.

Conclusion

Although hydroxychloroquine and chloroquine poisoning cases reported to the ToxIC Registry over the past ten years are rare, this report demonstrates the severity of toxicity due to these agents in cases managed by medical toxicologists and summarizes the therapies that may be used to manage such poisonings. This propensity toward severe effects warrants thorough evaluation and monitoring of all patients with hydroxychloroquine or chloroquine toxicity. We plan to continue to monitor these cases through the ToxIC Registry and report on trends in use of chloroquine and hydroxychloroquine as they continue.

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Declarations

Conflicts of Interest None

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