Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Epilepsy Research 165 (2020) 106399

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Assessing the risk of seizures with chloroquine or hydroxychloroquine therapy for COVID-19 in persons with epilepsy

Sandipan Pati[a,b,*], Thomas Houston[a,b]

[a] Department of Neurology, University of Alabama at Birmingham, AL, United States
[b] Epilepsy and Cognitive Neurophysiology Laboratory, University of Alabama at Birmingham, AL, United States

ARTICLE INFO

Keywords:
Chloroquine
Hydroxychloroquine
COVID-19
Epilepsy

ABSTRACT

Background: The goal of this systematic review is to assess the published literature for seizure risk with chloroquine or hydroxychloroquine therapy in persons with and without epilepsy. With the COVID-19 pandemic, there is a desperate need for treatment against the SARS CoV-2 virus. Chloroquine or hydroxychloroquine is one proposed medication that has received substantial public attention. However, the package insert states that these medications may provoke seizures in patients with epilepsy, and this has resulted in increased questions and anxiety in the epilepsy community.

Methods: PubMed (1970 to March 27, 2020) and the Embase (1970 to March 27, 2020) were searched with the terms chloroquine or hydroxychloroquine and seizure or epilepsy, convulsions, or status epilepticus. Selected studies were reviewed, and the adverse drug reaction was classified.

Results: Only eleven out of 31 studies were deemed eligible for systematic analysis. For chloroquine, eligible studies were- one prospective study(n = 109), two case series(n = 6), and six case reports. The dose of chloroquine ranged between 100 – 500 mg/day, except in one patient with a seizure, who was after taking 1000 mg. For hydroxychloroquine, there was one prospective observational study(n = 631) and one case report. The clinical trials failed to find any significant relation between seizures and chloroquine or hydroxychloroquine.

Conclusion: Although the package insert describes an increased risk of seizure, the systematic review highlights that such a statement is not supported by class I evidence. Clinicians, therefore, need to understand that data regarding this specific topic is limited to case series and case reports. There is no substantial evidence to suggest that these medications can increase seizure risk.

1. Introduction

With the global outbreak of coronavirus disease (COVID-19), laboratory-confirmed cases have increased explosively, with 227,368 deaths as of April 29, 2020 (WHO, 2020). A significant proportion of symptomatic patients required medical care, and some required specialized intensive care management that is overwhelming the health care system. Given the acute shortage of ventilators and personal protective equipment, there is a desperate need for therapy against the virus SARS CoV-2 - the pathogen for COVID-19 (Fauci et al., 2020). Among the different medications that are under trial, two antimalarial drugs- chloroquine and hydroxychloroquine have received substantial public attention because of positive results from small studies and media coverage(Cortegiani et al., 2020; Hu et al., 2020). Chloroquine (4-amino quinolone) is prescribed for treatment and chemoprophylaxis against malaria, while hydroxychloroquine is used to treat inflammatory conditions like lupus. A quick search in the clinicaltrials.gov with the term chloroquine or hydroxychloroquine for COVID-19 yielded over 30 studies as of early April 2020. Despite the lack of any substantial evidence to support efficacy, given the present crisis, many academic centers and physicians have incorporated these medications into their therapeutic armamentarium against COVID-19 (Cortegiani et al., 2020). The package insert for chloroquine and hydroxychloroquine states that “patients with a history of epilepsy should be advised about the risk of chloroquine or hydroxychloroquine provoking seizures.” Understandably this statement has stirred up increased questions and anxiety in the epilepsy community about the safety of chloroquine or hydroxychloroquine in persons with epilepsy. A preclinical study suggests that chloroquine can elicit seizures in a dose-related manner by inhibiting GABAergic neurotransmission

* Corresponding author at: Epilepsy and Cognitive Neurophysiology Laboratory, Department of Neurology, University of Alabama at Birmingham, CIRC 312 | 1719 6th Avenue South|, Birmingham, AL 35294, United States.
E-mail address: spati@uabmc.edu (S. Pati).

https://doi.org/10.1016/j.eplepsyres.2020.106399
Received 7 April 2020; Received in revised form 6 June 2020; Accepted 10 June 2020
Available online 11 June 2020
0920-1211/

Table 1
Characteristics of nine studies (six case reports, two case series, and one clinical trial).

Type of Adverse Reaction	Type of Study, level of evidence	Patient comorbidities	Drug/dose	Reason for prescript-tion	Seizures or status epilepticus (SE)	Country reported	References
Non dose related	Case Report, IV	49 yo, F, SLE	C, 250 mg/dX 30 d	SLE	multiple FIAS X24 hrs	Poland	2018. Krzeminski P, Lesiak A, Narbutt J.PMID: 30,206,460
Non dose related	Case Report, IV	14 yo, F, SLE	C, 500 mg/d	SLE	one BTC sz	Venezuela	2004 Tristano AG, Falcón L, Willson M, de Oca IM PMID: 14,740,170
dose related	Case Report, IV	30 yo,M, healthy	C, 1gm/d X4 d	Ppx	one BTC sz	UK	2016 Martin AN, Tsekes D, White WJ, Rossouw D. PMID: 27,005,796
Non dose related	Case Report, IV	35 yo,M, healthy	Savarine (C 100 mg + Proguanil 200 mg) -2 doses	Ppx	one BTC sz	France	2000. Schiemann R, Coulaud JP, Bouchaud O. PMID: 11179947.
Non dose related	Case Series, IV	40 yo M, healthy	Maloprim (C 400 mg + Dapsone 100 mg + Pyrimthemine 12.5 mg) 1 tab/wk X 4 wks	Ppx	two BTC sz	UK	1988, Fish DR, Espir ML. PMID: 3,139,186
		26 yo F, generalized epilepsy	Maloprim (C 400 mg + Dapsone 100 mg + Pyrimthemine 12.5 mg) 1 tab/wk X 3 wks	PPx	one BTC sz	UK	
		49 yo F, focal epilepsy	C 400 mg /d X 1 d	Ppx	prolonged BTC sz	UK	
Non dose related	Case eport, IV	42 yo, M, Leprosy	C 450 mg/d x 8 d	ENL (Leprosy)	two BTC szs	Nigeria	1998 Ebenso BE. PMID: 9,715,604
Non dose related	Prospective study during therapeutic clinical trial, II	N = 109; 9 mo-13 y, cerebral malaria	dose unknown, study correlated seizure with serun level of C and a metabolite	Ppx	54 % szs, 9% SE	Kenya	2000. Crawley J, Kokwaro G, Ouma D, Watkins W, Marsh K. PMID: 11,169,275
Non dose related	Case Series, IV	28 yo, F, SLE	C 200 mg/d X 180d	SLE	one BTC sz	Netherlands	1992. Luijckx GJ, De Krom MC, Takx-Kohlen BC. PMID: 1,344,765
		21,yo, M, healthy	C 300 mg /week X 2mo	Ppx	two BTC sz		
		23 yo, M, h/o one sz	C 300 mg /week X 2mo	Ppx	one BTC sz		
Non dose related	Case Report, IV	69 = 8 yo, F, healthy	C 100 mg/d X12 d	Ppx	NCSE	Switzerland	1995. Mülhauser P, Allemann Y, Regamey C.PMID: 7,762,925
Non dose related	Case Report,IV	17, yo,F, h/o, SLE, focal epilepsy	HC 200 mg/d X14 d	SLE	First onset BTC. prior h/o FIAS only.	Italy	2000 Malcangi G, Fraticelli P, Palmieri C, Cappelli M, Danieli MG.PMID: 11,149,659
Not applicable	Prospective observational study, II	N = 600 adults with newly diagnosed lupus and no prior h/o seizure	HC- specific dose not mentioned in the study	SLE	6.7 % (40) participants had a seizure after the diagnosis of SLE. Seizure details not mentioned in the manuscript	USA	2008. Andrade RM, Alarcon GS, Gonzalez LA et al. PMID: 17,875,548

F = female, M = male, C = chloroquine, HC = hydroxychloroquine, Ppx = prophylaxis, SLE = systemic lupus erythematous, ENL = erythema nodosum leprosum, FIAS = focal impaired awareness seizure, BTC = bilateral tonic-clonic seizure, CSF = cerebrospinal fluid.

(Amabeoku, 1992). In preclinical studies, a lower dose (1 – 5 mg/kg) of chloroquine prevents seizures, while a higher dose (10 – 50 mg/kg) had pro-convulsant effects (Hassanipour et al., 2016). In contrast to chloroquine, hydroxychloroquine has a lower incidence of CNS effects. The goal of this systematic review is to assess the published literature for seizure risk with chloroquine therapy in persons with and without epilepsy.

2. Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. PubMed (1970 to March 27, 2020) and the Embase (1970 to March 27, 2020) were searched with the terms chloroquine or hydroxychloroquine and seizure, epilepsy, convulsions, or status epilepticus. Only published abstracts and literature in English were reviewed. Inclusion criteria were any case study or series, and clinical trials reporting seizure or status epilepticus with chloroquine or hydroxychloroquine. Exclusion criteria were overdose or poisoning from chloroquine, animal studies, and reports of cardiac or neuropsychiatric adverse effects. Data extracted from the reports were -age, sex of study populations, the dosage of medication if available, and reported comorbidities. We reviewed the reported medication dosage to confirm that the adverse effects were related to an overdose. The level of evidence was graded between I-IV (Armstrong and Gronseth, 2018).

The adverse drug reaction of interest is a seizure or status epilepticus. For each selected study, the authors reviewed the entire manuscript and classified the adverse drug reaction as either– a) dose-related, b) non-dose related, c) dose-related and time-related, d)time-related, e) withdrawal or f) unexpected failure of therapy (Edwards and Aronson, 2000).

3. Results

Only eleven out of 31 studies were deemed eligible for systematic analysis. Preclinical studies or reports of chloroquine or hydroxychloroquine poisoning, cardiovascular and neuropsychiatric complications were excluded. For chloroquine, eligible studies were- one prospective study(n = 109), two case series(n = 6), and six case reports. For hydroxychloroquine, there was one prospective observational study (n = 631) and one case report (Table 1).

3.1. Risk in healthy individuals

3.1.1. Chloroquine

Pooled data revealed five healthy adults (all case reports and series) had a convulsive seizure after taking chloroquine for primary prophylaxis against malaria. One of the individuals had speech difficulties secondary to non-convulsive status epilepticus. The dose ranged between 100 mg–400 mg per day except for one individual who had a seizure after ingesting 1 gm chloroquine that was prescribed by a non-professional provider. In one individual, the EEG revealed generalized spike-wave epileptiform discharges, thereby suggesting underlying undiagnosed generalized epilepsy.

3.2. Risk in individuals with non-neurological illness

3.2.1. Chloroquine

Four adults (all case reports and series) had a convulsive seizure after taking therapeutic chloroquine for leprosy or lupus. The dose ranged between 200 – 500 mg/day. Two subjects in the case series had multiple laboratory investigations, including CSF analyses, and EEG that failed to identify any alternative etiology.

3.2.2. Hydroxychloroquine

A multi-center prospective observational study evaluating predictors of time-to-seizure occurrence in patients with newly diagnosed lupus (N = 600) confirmed a longer latency to seizure occurrence with the use of hydroxychloroquine thereby suggesting that the medication can protect against the development of seizure. Seizures were present in 6.7 % (40) of the participants.

3.3. Risk in individuals with neurological illness, including epilepsy

3.3.1. Chloroquine

To investigate the relationship between blood levels of chloroquine (used as prophylaxis), its metabolite desethylchloroquine, and seizures in children (N = 109, 9 months-13 years) with cerebral malaria, the investigators took advantage of a double-blinded randomized control trial where intramuscular phenobarbital (20 mg/kg) or placebo was given to prevent seizures. 54 % (59 out of 109) of children had seizures following cerebral malaria. There was no correlation between seizure and blood level of chloroquine or desethylchloroquine (Crawley et al., 2000). Three case studies documented seizure following chloroquine prophylaxis (300 – 400 mg/day) in persons with epilepsy.

3.3.2. Hydroxychloroquine

One young woman with a history of focal epilepsy and lupus had a tonic-clonic seizure for the first time following two weeks intake of therapeutic hydroxychloroquine 200 mg/day (5 mg/kg). Anti-seizure medications were unchanged, and laboratory investigations ruled out acute exacerbation of lupus. Following discontinuation of hydroxychloroquine, she had no further tonic-clonic seizures during follow up although focal seizures continued.

4. Discussion and conclusion

Both chloroquine and hydroxychloroquine have been used for over a decade in chemoprophylaxis against malaria and to treat lupus. Although the package insert states an increased risk of seizure, the systematic review highlights that such a statement is not supported by any class I studies but rather by anecdotal case reports and case series. Two clinical trials failed to demonstrate an increased risk of seizures with these medications.

The goal of this review was not to evaluate if chloroquine or hydroxychloroquine is an effective therapy against COVID-19. Clinical trials are ongoing, and many centers are offering the medication either through a clinical trial or as an off-label therapy. Of note, a recent observational study failed to establish the benefit of hydroxychloroquine against COVID-19 (Geleris et al., 2020). Many of our epilepsy patients reside at a group home or facility and are at risk of contracting SARS CoV-2 virus. The evidence evaluating a link between chloroquine or hydroxychloroquine and seizure is insufficient to suggest a significant correlation. Clinicians, therefore, need to understand that data regarding this specific topic is limited to case series and case reports. There is no substantial evidence to suggest that these medications can increase seizure risk.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106399.

References

Amabeoku, G., 1992. Involvement of GABAergic mechanisms in chloroquine-induced seizures in mice. Gen. Pharmacol. 23 (2), 225–229. https://doi.org/10.1016/0306-3623(92)90015-C.

Armstrong, M.J., Gronseth, G.S., 2018. Approach to assessing and using clinical practice

guidelines. Neurol. Clin. Pract. 8 (1), 58–61. https://doi.org/10.1212/CPJ.0000000000000417.
Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A., Einav, S., 2020. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J. Crit. Care 57, 279–283. https://doi.org/10.1016/j.jcrc.2020.03.005.
Crawley, J., Kokwaro, G., Ouma, D., Watkins, W., Marsh, K., 2000. Chloroquine is not a risk factor for seizures in childhood cerebral malaria. Trop. Med. Int. Health 5 (12), 860–864. https://doi.org/10.1046/j.1365-3156.2000.00658.x.
Edwards, I.R., Aronson, J.K., 2000. Adverse drug reactions: definitions, diagnosis, and management. Lancet 356 (9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9.
Fauci, A.S., Lane, H.C., Redfield, R.R., 2020. Covid-19 - navigating the uncharted. N. Engl. J. Med. 382 (13), 1268–1269. https://doi.org/10.1056/NEJMe2002387.
Geleris, J., Sun, Y., Platt, J., Zucker, J., Baldwin, M., Hripcsak, G., Labella, A., Manson, D.K., Kubin, C., Barr, R.G., Sobieszczyk, M.E., Schluger, N.W., 2020. Observational study of Hydroxychloroquine in hospitalized patients with Covid-19. N. Engl. J. Med. https://doi.org/10.1056/nejmoa2012410.
Hassanipour, M., Shirzadian, A., Boojar, M.M.A., Abkhoo, Aminreza, Abkhoo, Alireza, Delazar, S., Amiri, S., Rahimi, N., Ostadhadi, S., Dehpour, A.R., 2016. Possible involvement of nitrergic and opioidergic systems in the modulatory effect of acute chloroquine treatment on pentylenetetrazol induced convulsions in mice. Brain Res. Bull. 121, 124–130. https://doi.org/10.1016/j.brainresbull.2015.11.020.
Hu, T.Y., Frieman, M., Wolfram, J., 2020. Insights from nanomedicine into chloroquine efficacy against COVID-19. Nat. Nanotechnol. 15 (4), 247–249. https://doi.org/10.1038/s41565-020-0674-9.
WHO, 2020. Coronavirus Disease 2019 (COVID-19) Situation Report-61. World Health Organizationhttps://doi.org/10.1001/jama.2020.2633.