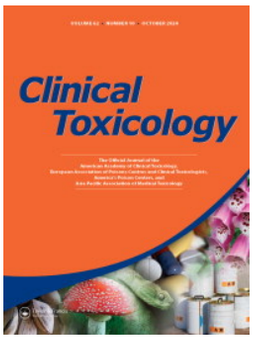


Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ictx20

The use of lipid emulsion therapy in severe hydroxychloroquine overdose – a narrative review of case reports

Erwin Schieveen, Femke M. J. Gresnigt & Chantal den Haan

To cite this article: Erwin Schieveen, Femke M. J. Gresnigt & Chantal den Haan (08 Oct 2024): The use of lipid emulsion therapy in severe hydroxychloroquine overdose – a narrative review of case reports, Clinical Toxicology, DOI: 10.1080/15563650.2024.2407059

To link to this article: https://doi.org/10.1080/15563650.2024.2407059

View supplementary material

Published online: 08 Oct 2024.

Submit your article to this journal

Article views: 143

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ictx20

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2024.2407059

Taylor & Francis
Taylor & Francis Group

Check for updates

REVIEW

The use of lipid emulsion therapy in severe hydroxychloroquine overdose – a narrative review of case reports

Erwin Schieveen[a], Femke M. J. Gresnigt[a,b] and Chantal den Haan[c]

[a]Emergency Department, OLVG Hospital, Amsterdam, The Netherlands; [b]Dutch Poison Information Center (DPIC), UMC Utrecht, University Utrecht, Utrecht, The Netherlands; [c]Department of Research & Epidemiology, OLVG Hospital, Amsterdam, The Netherlands

ABSTRACT

Introduction: Hydroxychloroquine has cardiac and cerebral sodium channel- and human ether-à-go-go-related gene (HERG) potassium channel-blocking effects. This causes depolarization delays, resulting in cardiovascular toxicity with potentially fatal consequences. Despite several supportive care options, hydroxychloroquine poisoning remains difficult to treat. Its high lipid solubility suggests that lipid emulsion therapy might be beneficial; however, no clear evidence regarding its efficacy is available. The aim of this review is to assess the evidence, the outcomes, and adverse events regarding the use of intravascular lipid emulsion therapy as a treatment for hydroxychloroquine poisoning.

Methods: We conducted a systematic search in PubMed, Embase.com, Cochrane Central Register of Controlled Trials (CENTRAL)/Wiley, Web of Science Core Collection/Clarivate Analytics, and Scopus/Scopus.com from inception until 1 November 2023. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria encompassed original observational or interventional studies, case series and case reports describing patients receiving lipid emulsion therapy for hydroxychloroquine toxicity. We extracted clinical data and performed a quality assessment of the included cases. We present the results as a narrative synthesis.

Results: Of 157 identified articles, 16 case reports met the inclusion criteria, reporting on 18 patients. Lipid emulsion therapy was always associated with additional treatments, and detailed information on the circumstances regarding the administration of intravenous lipid emulsion and its presumed effect was often lacking. Fifteen of 18 patients survived to hospital discharge. Some reports described clear and almost immediate clinical improvement after intravenous lipid emulsion administration. No clear adverse effects were reported.

Discussion: A limitation is the reliance on case reports, which varied in the degree of reported details. The administration of multiple therapeutic drugs in most cases made it difficult to attribute survival primarily to lipid emulsion. Publication bias may favour cases with successful outcomes.

Conclusion: Among published case reports, most patients who received lipid emulsion for treatment of hydroxychloroquine poisoning survived. The risk of bias, the small number of reports, and the lack of systematic reporting of both favourable and adverse effects limit any conclusions about the effectiveness of lipid emulsion for hydroxychloroquine poisoning.

ARTICLE HISTORY
Received 3 April 2024
Revised 15 September 2024
Accepted 16 September 2024

KEYWORDS
Case reports; hydroxychloroquine; intravenous lipid emulsion therapy; review; treatment

Introduction

Lipid emulsion therapy is well known as an antidote for local anaesthetic systemic toxicity [1–4]. Its mechanism of effect is most often described using the "lipid sink" or "lipid shuttle" theory, which suggests that lipophilic drugs are caught and contained by the lipid emulsion and redistributed towards the liver and skeletal muscle. This lowers the effective plasma concentration and protects organs prone to toxicity [1,5]. This process relies on the target drug being lipophilic, which is quantified using the lipid solubility coefficient. This coefficient is determined by calculation of the log [octanol/water partition]. For example, many local anaesthetic drugs like lidocaine and bupivacaine have a relatively high lipid solubility coefficient of 2.44 [6] and 3.41 [7], respectively.

This suggests that intravascular lipid emulsion therapy may also have detoxifying properties for other lipophilic medications, such as hydroxychloroquine [4,8–10], which has a lipid solubility coefficient of 3.6 [11]. Hydroxychloroquine is used as an antimalarial and antirheumatic drug and for the treatment of lupus erythematosus. In recent years, it became widely known during the SARS-CoV-19 pandemic when it was proposed as a potential treatment for COVID-19 [12]. Hydroxychloroquine has cardiac and cerebral sodium channel- and human ether-à-go-go-related gene (HERG) potassium channel-blocking effects. This causes depolarization delays [13,14], resulting in cardiovascular toxicity with potentially fatal consequences. Despite several supportive care options, hydroxychloroquine poisoning remains difficult to treat. Its high lipid solubility suggests that lipid emulsion therapy might be beneficial; however, no clear evidence regarding its efficacy is available.

CONTACT Femke M.J. Gresnigt f.m.j.gresnigt@olvg.nl Emergency Department, OLVG Hospital, Oosterpark 9, Amsterdam, 1091 AC, The Netherlands.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2024.2407059.
© 2024 Informa UK Limited, trading as Taylor & Francis Group

The aim of this review is to assess the evidence, outcomes, and adverse events regarding the use of intravascular lipid emulsion therapy as a treatment for hydroxychloroquine poisoning.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [15] in conducting this review, which was not pre-registered or financially supported.

Search strategy

An information specialist (CH) performed the systematic search and searched the databases of PubMed, Embase.com, Cochrane Central Register of Controlled Trials (CENTRAL)/Wiley, Web of Science Core Collection/Clarivate Analytics and Scopus/Scopus.com from inception until 1 November 2023. The following terms, including synonyms and closely related words, were used as index terms or free-text words: "hydroxychloroquine" and "intravenous fat emulsion". Full search strategies for all databases are available (Supplementary Appendix A). All titles identified in the search were independently screened by two reviewers (ES and FG) using Rayyan Systems, Inc. [16]. If any of the reviewers identified a title for full-text screening, it was included. Thereafter, full-text copies of all potentially relevant studies were acquired and independently evaluated by the two reviewers. If full-text screening resulted in conflict, open discussion and in-depth review of the article occurred to decide upon inclusion. All articles included for full-text screening were reference searched.

Inclusion/exclusion criteria

All original reports of observational studies (case reports, case series, cohort, case-control, cross-sectional) or interventional studies (randomized controlled trials, experimental studies) that enrolled patients who received lipid emulsion therapy for hydroxychloroquine toxicity were included. Reviews, letters to the editor without a new case description, and animal or *in vitro* studies were excluded. No study was excluded based on language or methodological quality. The primary outcome was immediate survival. Secondary outcomes included adverse effects.

Data extraction strategy

Data relating to study design, gender, age, symptoms, treatment and outcome were extracted. If multiple publications reported the same patient, the information was mined and described as a single study while listing all other publications.

Quality assessment and methods of analysis/synthesis

Since only case reports were included in the study, quality assessment for all studies resulted in a high risk of bias. The results are presented in Table 1 and as a narrative summary. Since only case reports were available, data were not pooled, and a meta-analysis was not possible.

Results

The search strategy produced 157 articles, of which 85 remained after eliminating duplicates (Figure 1). A total of 16 articles reporting on 18 patients were included in this review (Table 1). The reference search did not yield any additional articles. The included patients were quite homogenous, with 17 of 18 patients being young females with a mean age of 28 years. One-third of patients were 18 years of age or younger. The median ingested amount was 10 g ($n = 17$; IQR 5.5–20 g). Twelve patients presented with hypotension. Other symptoms included altered mental status, hypokalaemia, QRS complex prolongation, QTc interval prolongation, and ventricular dysrhythmias (Table 2). Most patients received sodium bicarbonate (15/18 patients), diazepam (15/18 patients) or epinephrine (15/18 patients) (Table 3).

Lipid emulsion therapy was always accompanied by additional treatments. Three cases mentioned the exact time of lipid emulsion therapy and the time of hydroxychloroquine ingestion; therapy was initiated 2 h [25], 6 h [17], and 15 h post-ingestion [29]. The timing of improvement of cardiovascular symptoms was mentioned in eight patients; no objective data were given in any case, but qualitative words such as "immediate", "within minutes", "a few minutes", "fast", and "quick" were most often used. Recurring hemodynamic instability and/or dysrhythmias were described in eight cases. In half of these cases, only one recurrence was described; in two out of eight cases, dysrhythmias/haemodynamic instability reoccurred on two or more occasions and in two cases, the exact rate of occurrence was not described. Two patients with these recurring cardiac symptoms were treated with subsequent lipid emulsion boluses, which was successful in preventing a recurrence in one case [19]; the other patient required an additional bolus [26]. A transient increase in lipase activity and C-reactive protein concentration, as well as increased aminotransferase activity, was the only reported complication related to lipid emulsion, which resolved without treatment in the patient who showed no clinical signs of pancreatitis [26]. The case report did not provide specific data on aminotransferase or lipase activities. Out of the 18 patients included, 15 survived to discharge. The three deceased patients had no difference in median age or median ingested hydroxychloroquine dose compared to patients who survived. A total of six patients received cardiopulmonary resuscitation, three of whom did not survive. Two patients were treated with intravenous lipid emulsion therapy following initially successful resuscitations. However, despite all treatments initiated, both patients experienced recurrent cardiac arrests. Subsequent cardiopulmonary resuscitation attempts were unsuccessful on the second and third attempts, respectively [30]. The other deceased patient died three days later due to multi-organ failure; the timing of administration of lipid emulsion therapy and cardiopulmonary resuscitation

Table 1. Description of patients reported.

Author, year	Age years/ sex	Dose hydroxychloroquine	Co-ingestions	Presenting symptoms	Other therapy given	Time and dose of intravenous lipid emulsion	Assumed response	Outcome
Alsufyani and King [17]	16 Female	9 g	–	Pulseless ventricular tachycardia after 1 h. Potassium concentration 1.6 mmol/L	Cardiopulmonary resuscitation with defibrillation 2x, endotracheal intubation, intravenous epinephrine bolus*, sodium bicarbonate*, diazepam 2 mg/kg intravenous bolus. Post cardiopulmonary resuscitation: phenylephrine 80 µg, high dose norepinephrine*, high dose epinephrine*, and diazepam 2 mg/kg/day. Effect: normalization of blood pressure*. Potassium remained low despite potassium chloride* supplementation	Intravenous lipid emulsion 6 h post-ingestion Dose*	"Immediate" increase in systolic blood pressure of 30 mmHg Complicated intensive care unit course, extubated after 2 weeks	Survived
Berkel and Taylor [18]	46 Female	0.8 g	Ethanol (serum concentration 2,800 mg/L)	Hypotension 92/63 mmHg. After 50 min; frequent episodes of ventricular tachycardia and torsade de pointes, QTc interval 837 ms	Ondansetron 4 mg intravenously and activated charcoal, ventricular tachycardia successfully terminated with sodium bicarbonate 50 mEq intravenously and magnesium sulfate 4g intravenously, midazolam 0.5 mg/h	Time* intravenous lipid emulsion 0.1 mL/kg/h, total dose not described, continued for 12 h.	No additional dysrhythmias occurred	Survived
Cole et al. [19]***	51 Female	12 g	Oxycodone 175 mg and paracetamol 11,375 mg ingested	Blood pressure 80/44 mmHg. Supposed ventricular fibrillation with spontaneous recovery, potassium concentration 2.2 mmol/L, hypomagnesaemia*	Naloxone*(no effect), endotracheal intubation, epinephrine 0.25 µg/kg/min, diazepam 150 mg total, electrolyte replacement*, vasopressin 0.04 U/min	Time* 20% intravenous lipid emulsion 100 mL bolus. After initial improvement; again systolic blood pressure <80 mmHg for which another bolus 900 mL 20% intravenous lipid emulsion in 30 min	"Immediate" haemodynamic improvement; blood pressure recovered to 115/66 mmHg in 5 min. During second intravenous lipid emulsion bolus blood pressure normalized and the patient awoke, for which sedative medication was given	Survived
Holvoet et al. [20]	54 Female	18 g	–	Hypotensive*, Glasgow coma scale 5, QTc interval prolongation*, 4 h later atrial fibrillation and QRS complex widening	Sodium bicarbonate 150 mL 8.4%, endotracheal intubation, diazepam 0.04 mg/kg/h	Time* 20% intravenous lipid emulsion 100mL	No clear response after intravenous lipid emulsion: ventricular fibrillation for which cardiopulmonary resuscitation was performed (successful), biventricular failure despite norepinephrine 0.6 µg/kg/min and dobutamine 10 µg/kg/min. Developed pulmonary oedema. Veno-arterial extracorporeal membrane oxygenation for 4 days, recurring ventricular tachycardia treated with isoproterenol 2 µg/min	Survived

(*Continued*)

Table 1. Continued.

Author, year	Age years/ sex	Dose hydroxychloroquine	Co-ingestions	Presenting symptoms	Other therapy given	Time and dose of intravenous lipid emulsion	Assumed response	Outcome
Hurley and Hanlon [21]	34 Female	*	*	Hypotensive* and seizures	*	Time* Dose*	Clinical improvement "within a few minutes after administration", details not specified.	Survived
McBeth et al. [22]	23 Female	40 g	–	Blood pressure 92/60 mmHg, QRS complex 140 ms, QTc interval 576 ms, 3 h later obtunded*, potassium concentration 1.5 mmol/L	After 3 h endotracheal intubation, fluids*, vasopressor support*, gastric lavage, activated charcoal. 3 h later severe haemodynamic instability with ventricular tachycardia and ventricular fibrillation (18x defibrillation), intravenous diazepam 60 mg bolus and 6 mg/h infusion, epinephrine 20 µg/min, norepinephrine 30 µg/min, sodium bicarbonate 30 mmol/h, magnesium 1 g/h infusion, potassium chloride 380 mmol	20% intravenous lipid emulsion 1.5 mL/kg bolus, infusion in 30 min (total dose 500 mL). Intravenous lipid emulsion given during dialysis, exact time not specified	Improvements on haemodynamics were seen, time and details not specified. Extubated on day 3, released from intensive care unit on day 6	Survived
Murphy et al. [23]	26 Female	4 g	Ethanol concentration 1,250 mg/L Methadone positive drug screen	Blood pressure 53/40 mmHg, altered Glasgow Coma Scale*, QRS complex 129 ms, QTc interval 605ms, premature ventricular contractions, potassium concentration 1.6 mmol/L	Intubation, fluids*, epinephrine boluses*, norepinephrine boluses*, epinephrine infusion, sodium bicarbonate 2 ampules bolus and infusion*, intravenous magnesium* (no effect), potassium chloride*, activated charcoal, hydrocortisone*	Time* 20% intravenous lipid emulsion 1.5 mL/kg bolus in 1min and 0.25 mL/kg/min for 1 h	Blood pressure normalized, time not specified. Torsade de pointes after intravenous lipid emulsion, for which magnesium intravenous was given. Complicated intensive care course	Survived
Ndukwu and Ghahramani [24]	20 Female	60 g	–	Glasgow Coma Scale 4, marked hypokalemia*, hypocalcemia*, toxic hydroxychloroquine concentrations*, QTc interval 600 ms, runs of torsade de pointes	Gastric decontamination*, intravenous magnesium*, intravenous calcium*, potassium chloride* and amiodaron*. Remained haemodynamic unstable with torsade de pointes runs	Time* Dose*	Haemodynamic stabilization and return to sinus rhythm "within minutes after intravenous lipid emulsion initiation."	Survived
Noda et al. [25]	17 Female	10 g	–	Vomiting, pain*, Glasgow Coma Scale 14, blood pressure 85/52 mmHg, heart rate 85 beats/min, lactate concentration 2.7 mmol/L, potassium concentration 2.9 mmol/L, multiple premature ventricular contractions	Fluids*, potassium* chloride*, dobutamine*, olprinone*	15 h post-ingestion, intravenous lipid emulsion 1.5 mL/kg intravenous bolus	4 h later haemodynamic stability; blood pressure 110/60 mmHg, regaining urine production	Survived

(*Continued*)

Table 1. Continued.

Author, year	Age years/ sex	Dose hydroxychloroquine	Co-ingestions	Presenting symptoms	Other therapy given	Time and dose of intravenous lipid emulsion	Assumed response	Outcome
Onsia and Bots [26]	35 Female	20 g	–	Vomiting, malaise and blood pressure 90/59 mmHg. potassium concentration 3.4 mmol/L QRS complex widening*, ventricular tachycardia and ventricular fibrillation; self-limiting	Sedation with propofol* and midazolam*, intubation, potassium* chloride* and magnesium*	Time*, A bolus of 1.5 mL/kg of 20% intravenous lipid emulsion. On the third day: Repeat bolus of intravenous lipid emulsion, followed by a subsequent infusion of 0.25 mL/kg/min of 20% during 1 h	First bolus: Initial cardiac stabilization but subsequently cardiac dysrhythmias reoccurred, ranging from ventricular tachycardia with pulse to ventricular fibrillation, for which cardiopulmonary resuscitation (for only 10 sec), with a "fast" normalization. Second/third bolus: "Quick" normalization of cardiac rhythm (bigeminy/trigeminy)	Survived
Rush et al. [27]	16 Female	4 g	–	Lightheadedness, ventricular tachycardia, cardiac arrest	30 min of cardiopulmonary resuscitation, vasopressor* support. Sodium bicarbonate*, diazepam* Later phenobarbital infusion*	Time* Dose*	Recurrent tachycardia arrests which resolved with increased alkalinization	Survived
Suen and Harding [28]	16 Female	24 g		Tachycardia, altered mental status*, followed by ventricular tachycardia, pulseless ventricular tachycardia and ventricular fibrillation. Hyper-hypokalaemia*, hypocalcaemia*, acidaemia*, increased lactate concentration*, hypoxic ischaemic encephalopathy and multisystem organ failure	Defibrillation; return of spontaneous circulation after 17 min of cardiopulmonary resuscitation, endotracheal intubation. Epinephrine*, magnesium*, calcium*, sodium bicarbonate*, amiodarone*. Midazolam and fentanyl infusion*. Later: high dose diazepam*, vasopressor supports*, activated charcoal, lidocaine*	Time* Dose*	No clear effect: Again cardiac arrest, 45 min cardiopulmonary resuscitation and veno-arterial extracorporeal membrane oxygenation	Died 3 days post-ingestion
ten Broeke et al. [29]	25 Female	17.5g	Diazepam (ingested 550 mg)	QRS complex widening*, potassium concentration 2.7 mmol/L, unconscious*, hypotension* and apnoea	Endotracheal intubation, norepinephrine*, potassium chloride 40 mmol, diazepam 2 mg/kg/24h, sodium bicarbonate 100 mL 8.4%	Time* 20% intravenous lipid emulsion 1.5 mL/kg bolus and 0.25 mL/kg/min for 30 min total 400 mL	Haemodynamic stability was established "within a few hours"	Survived
ten Broeke et al. [29]	25 Male	5 g	Codeine (ingested 10 mg) Domperidone (ingested 10 mg)	QTc interval 580 ms and potassium concentration 2.7 mmol/L	Diazepam 2 mg/kg/24h, potassium chloride*, sodium bicarbonate 100 mL 8.4%	2h post-ingestion: 20% intravenous lipid emulsion, 1.5 mL/kg bolus and 0.25 mL/kg/min for 30 min (total 400 mL)	Remained haemodynamically stable	Survived
Wong et al. [30]	37 Female	6 g	Chloroquine (ingested 6.25 g)	Blood pressure 75/41 mmHg, heart rate 104 beats/min, QRS complex 172 ms, potassium concentration 2.5 mmol/L, torsade de pointes, ventricular fibrillation successfully converted with cardiopulmonary resuscitation, another cardiac arrest after 3 h	Fluids*, sodium bicarbonate 8.4% repeated doses*. Epinephrine infusion 10 µg/min, endotracheal intubation, activated charcoal, diazepam 2x (10 mg bolus and 10 mg/h infusion, increased after second cardiopulmonary resuscitation to 15 mg/h)	During second cardiopulmonary resuscitation: 20% intravenous lipid emulsion 100 mL in 3 min	No effect	Died 12 h post-ingestion

(*Continued*)

Table 1. Continued.

Author, year	Age years/ sex	Dose hydroxychloroquine	Co-ingestions	Presenting symptoms	Other therapy given	Time and dose of intravenous lipid emulsion	Assumed response	Outcome
Wong et al. [30]	29 Female	20 g	Prednisolone (unknown amount ingested)	Glasgow Coma Scale 5, QRS complex 156 ms; later 200 ms, potassium concentration 3.3 mmol/L, shock*, cardiac arrest with 5 min cardiopulmonary resuscitation	Endotracheal intubation, activated charcoal, fluids*, sodium bicarbonate 100 mL 8.4%, later repeated, epinephrine infusion*, potassium chloride*, diazepam 50 mg bolus and 5 mg/h infusion	After first cardiopulmonary resuscitation: 10% intravenous lipid emulsion 100 mL bolus, followed by 400 mL in 30 min	No clear effect: Another cardiac arrest wide complex tachycardia, second cardiopulmonary resuscitation successful, another cardiac arrest soon after; third cardiopulmonary resuscitation unsuccessful	Died 5.5 h post-ingestion
Ying and Wong**[31]	18 Female	6 g		Altered mental status*, blood pressure 63/37 mmHg, heart rate 68 beats/min, potassium concentration 1.5 mmol/L. QTc interval 540ms.	Epinephrine*, endotracheal intubation, propofol*, electrolyte repletion* continuous kidney replacement therapy.	Time* Dose*	No direct effects described, extubation after 3 days	Survived
Zambratto et al.**[32]	18 Female	6–8 g		Hypotension 67/37 mmHg, heart rate 60 beats/min, QTc interval 540ms. Acidotic*, potassium concentration 1.5 mmol/L	Intubation, midazolam*, diazepam*, epinephrine*, octreotide*, continuous kidney replacement therapy	Time* Dose*	No direct effects described, extubation after 6 days	Survived

*Not specified/unknown.
**Both case reports come from the same hospital and are published around the same time, with a highly similar case presentation. This raised the suspicion that both cases are based on the same patient, thus being a duplicate in this study. Sadly, none of the authors could be contacted to verify this. Since not all variables were exactly the same, both cases are presented.
***Considered a duplicate article based on the same case with Stellpflug et al. [33]; therefore, only one case was included for analysis.

was unknown. Of the three patients who survived after cardiopulmonary resuscitation, only in one case was the timing of lipid emulsion specified, which was 5 h after performing resuscitation [17]. Two of the three deceased patients presented with a co-ingestion (chloroquine, prednisolone) compared to five of the fifteen surviving patients (ethanol, oxycodone, paracetamol, diazepam, codeine, domperidone).

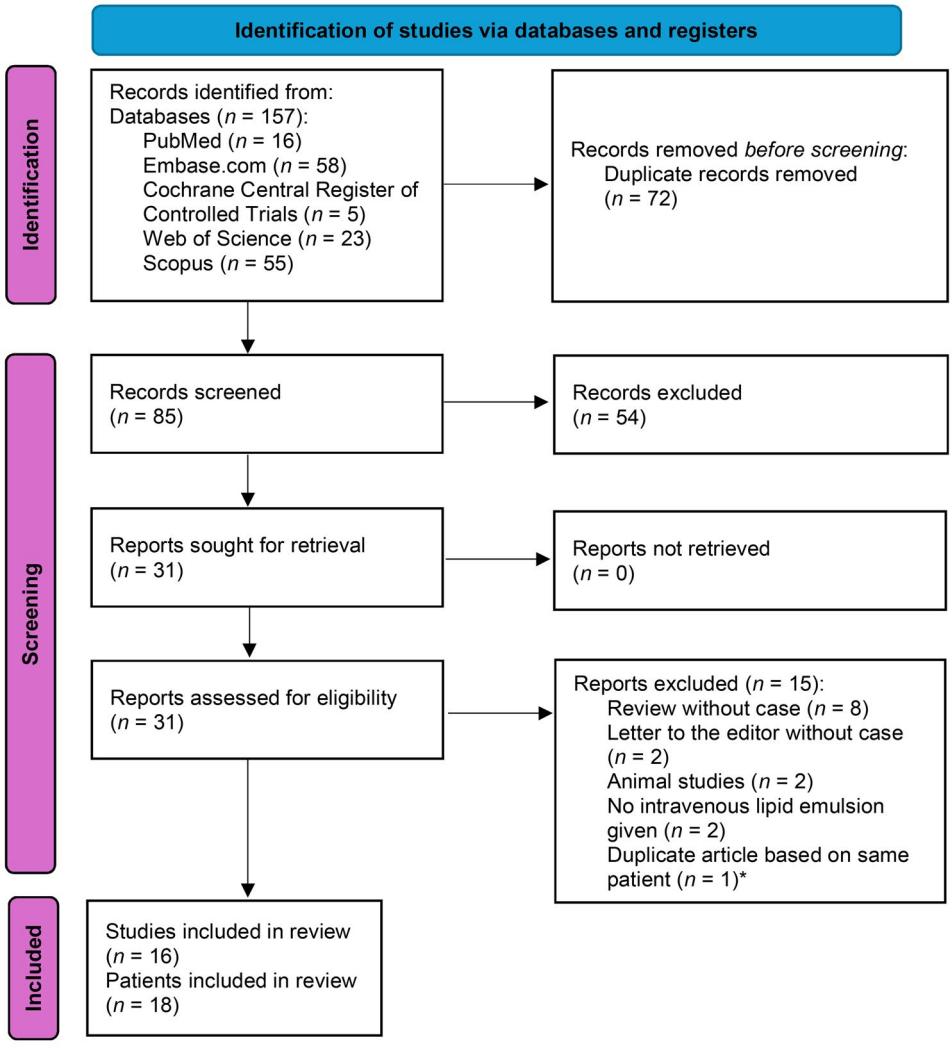
Discussion

We analyzed 18 case reports that provided data relevant to the use of lipid emulsion therapy for hydroxychloroquine overdose. Some case reports described clear and rapid clinical improvement shortly after the use of intravenous lipid emulsion, while others demonstrated no apparent effect with sometimes recurring hemodynamic instabilities and dysrhythmias. Adverse effects following the administration of intravenous lipid emulsion were infrequently reported.

Some of the available case reports suggest the benefit of intravenous lipid emulsion use with infrequent complications. Other studies cautiously seem to support the proposed pharmacodynamic and pharmacokinetic effects of intravenous lipid emulsion on lipid-soluble drugs, including hydroxychloroquine [8,9, 34–36]. Additional treatments employed in each instance render the direct effects of intravenous lipid emulsion challenging to interpret. One of the deceased patients received lidocaine concomitantly with intravenous lipid emulsion, possibly limiting the effects on hydroxychloroquine intoxication. However, the proposed pharmacodynamics of these interactions remain theoretical.

While the findings suggest the potential utility of intravenous lipid emulsion, some considerations arise when analyzing these results. Several other reports of comparable severe hydroxychloroquine poisonings also illustrate survival without the use of intravenous lipid emulsion [13, 37–40], suggesting no additional effect by intravenous lipid emulsion. Additionally, adverse effects of intravenous lipid emulsion should be considered. In the cases included in this review, only one patient demonstrated an increased lipase activity and C-reactive protein concentration, which was thought to be due to self-limiting pancreatitis secondary to intravenous lipid emulsion administration. The included case reports likely do not consistently report possible adverse effects of intravenous lipid emulsion. Any adverse effects mentioned may underestimate their true likelihood. Although adverse events were rarely described in these cases, other studies reported effects that were life-threatening or interfered with other treatments. Examples of adverse effects after lipid emulsion therapy include pancreatitis, acute respiratory distress syndrome, fluid overload, and lipaemia interfering with laboratory tests and continuous renal replacement therapy [10–12, 38, 41,42]. Nonetheless, attributing an adverse effect to a single treatment given simultaneously with other treatments in an acute setting is difficult.

Also, assessing the efficacy of intravenous lipid emulsion in critically ill patients might be challenging due to potential changes in pharmacokinetics in critically ill patients. Acidosis could significantly alter the pharmacodynamics of treatments. Using Log P to determine drug lipophilicity may not



[17]* Cole JB, Stellpflug SJ, Smith SW. Refractory Hypotension and "Ventricular Fibrillation" With Large U Waves After Overdose. JAMA Intern Med. 2016 ;176(7):1007-9. DOI: 10.1001/jamainternmed.2016.2065.
[18]* Stellpflug SJ, Floan AJ, Lee SC, Cole J. Hydroxychloroquine overdose treated successfully with intravenous fat emulsion. Clin. Toxicol. 2013;51(7) 652-652. DOI: 10.3109/15563650.2013.817658

Figure 1. Identification of studies.

accurately reflect lipid solubility in patients, as it does not account for ionized drugs. Additionally, the pH used for Log P calculations may not match patient conditions. Mullins and colleagues [43] suggest using Log D at pH 7.0, which might be more appropriate. Hydroxychloroquine has a Log D of 1.08, lidocaine 0.83, and bupivacaine 2.45 at pH 7.0 [41]. At this pH, bupivacaine remains highly lipophilic, whereas hydroxychloroquine and especially lidocaine become relatively more hydrophilic. Thus, the effectiveness of intravenous lipid emulsion in bupivacaine toxicity may differ from its effectiveness in hydroxychloroquine poisoning and could depend on pH status or other patient parameters.

Limitations

The review comprises a limited number of case reports, with variability in data quality and completeness, hindering the ability to draw definitive conclusions. Many of these case reports lacked essential details regarding the administration of intravenous lipid emulsion and its assumed effects. Also, the variety of case presentations and the simultaneous administration of other medications introduce complexity in attributing observed effects solely to lipid emulsion therapy. Publication bias may also favour cases with successful outcomes.

Conclusion

Among published case reports, 15 out of 18 patients who received lipid emulsion for treatment of hydroxychloroquine poisoning survived. The only reported adverse event concerned transiently increased lipase activity and C-reactive protein concentration in a patient without any clinical signs of pancreatitis. Reporting bias, the small number of reports, heterogeneous reporting of both favourable and adverse effects and the lack of controls each limit conclusions about the effectiveness of lipid emulsion for hydroxychloroquine poisoning.

Table 2. Reported symptoms among the 18 patients analysed in the review.

Symptoms	*n*
Cardiovascular symptoms	
"Hypotension"*	14
Pulseless ventricular tachycardia/ ventricular tachycardia	9
QTc interval prolongation (>450 ms)	8
Cardiac arrest	5
Torsade des pointes	5
QRS complex prolongation (>100 ms)	4
Premature ventricular contractions	2
Atrial fibrillation	1
Bradycardia (<60 beats/min)	1
"Shock"*	1
Spontaneous recovery ventricular fibrillation	1
Tachycardia (>100 beats/min)	1
Gastrointestinal symptoms	
Vomiting	2
Pain	1
Laboratory abnormalities	
"Hypokalaemia"*	12
"Hypocalcaemia"*	2
"Elevated lactate concentration"*	2
"Acidosis"*	2
"Hypomagnesaemia"*	1
Neurological symptoms	
Altered mental status/unconsciousness/decreased Glasgow Coma Scale	9
Seizures	1
Hypoxic ischaemic encephalopathy	1
Other symptoms	
Malaise	1
Apnoea	1

Symptoms are mentioned as described in the case reports.
*Specific values are not always mentioned in the case reports.

Table 3. Overview of treatment given to the 18 patients.

Treatment	*n*
Sodium bicarbonate intravenously	16
Diazepam intravenously	12
Epinephrine intravenously	11
Potassium intravenously and orally*	9
Activated charcoal orally	6
Magnesium intravenously	6
Midazolam intravenously	4
Norepinephrine intravenously	4
Amiodarone intravenously	3
Calcium intravenously	2
Propofol intravenously	2
Continuous kidney replacement therapy	2
Ondansetron intravenously	1
Hydrocortisone intravenously	1
Phenylephrine intravenously	1
Vasopressin intravenously	1
Dobutamine intravenously	1
Olprinone intravenously	1
Fentanyl intravenously	1
Lidocaine intravenously	1
Octreotide intravenously	1
Naloxone intravenously	1

*Route of administration not always specified in reported cases.

Authors' contributions

FG and ES contributed equally; they conceived the study, designed the trial, and provided the draft of the research protocol. All authors contributed substantially to the revision of the research protocol. CH was responsible for performing the search, collecting the articles and managing the selection process. FG advised on the study design, and FG and ES performed the study selection and extracted the data. FG, ES and CH drafted the manuscript. All authors contributed substantially to its revision. FG and ES take full responsibility for the paper as a whole.

Disclosure statement

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors reported there is no funding associated with the work featured in this article.

ORCID

Femke M. J. Gresnigt http://orcid.org/0000-0002-6428-8600
Chantal den Haan http://orcid.org/0000-0002-2640-3946

Data availability statement

Data available on request from the authors.

References

[1] Ok SH, Hong JM, Lee SH, et al. Lipid emulsion for treating local anesthetic systemic toxicity. Int J Med Sci. 2018;15(7):713–722. doi: 10.7150/ijms.22643.
[2] Neal JM, Barrington MJ, Fettiplace MR, et al. The third American Society of Regional Anesthesia and Pain Medicine practice advisory on local anesthetic systemic toxicity: executive summary 2017. Reg Anesth Pain Med. 2018;43(2):113–123. doi: 10.1097/AAP.0000000000000720.
[3] Lavonas EJ, Drennan IR, Gabrielli A, et al. Part 10: special circumstances of resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18 Suppl 2):S501–S18. doi: 10.1161/CIR.0000000000000264.
[4] Paneta M, Waring WS. Literature review of the evidence regarding intravenous lipid administration in drug-induced cardiotoxicity. Expert Rev Clin Pharmacol. 2019;12(7):591–602. doi: 10.1080/17512433.2019.1621163.
[5] Fettiplace MR, Weinberg G. The mechanisms underlying lipid resuscitation therapy. Reg Anesth Pain Med. 2018;43(2):138–149. doi: 10.1097/AAP.0000000000000719.
[6] National Center for Biotechnology Information. PubChem compound summary for CID 3676, lidocaine. https://pubchem.ncbi.nlm.nih.gov/compound/3676.
[7] National Center for Biotechnology Information. PubChem compound summary for CID 2474, bupivacaine. https://pubchem.ncbi.nlm.nih.gov/compound/2474.
[8] Tse C, Chan Y, Lau F. Intravenous lipid emulsion as antidote: experience in Hong Kong. Hong Kong J Emerg Med. 2015;22(2):100–107. doi: 10.1177/102490791502200204.
[9] Tampakis K, Vogiatzakis N, Kontogiannis C, et al. Intravenous lipid emulsion as an antidote in clinical toxicology: a systematic review. Eur Rev Med Pharmacol Sci. 2020;24(12):7138–7148. doi: 10.26355/eurrev_202006_21708.
[10] Lee SH, Kim S, Sohn JT. Lipid emulsion treatment for drug toxicity caused by nonlocal anesthetic drugs in pediatric patients: a narrative review. Pediatr Emerg Care. 2023;39(1):53–59. doi: 10.1097/PEC.0000000000002828.
[11] National Center for Biotechnology Information. PubChem compound summary for CID 3652, hydroxychloroquine. https://pubchem.ncbi.nlm.nih.gov/compound/3652.
[12] Doudka N, Giocanti M, Basso M, et al. Development and validation of a simple and rapid ultrahigh-performance liquid chromatogra-

phy tandem spectrometry method for the quantification of hydroxychloroquine in plasma and blood samples in the emergency context of SARS-CoV-2 pandemic. Ther Drug Monit. 2021;43(4):570–576. doi: 10.1097/FTD.0000000000000836.
[13] de Olano J, Howland MA, Su MK, et al. Toxicokinetics of hydroxychloroquine following a massive overdose. Am J Emerg Med. 2019;37(12):2264.e5-2264–e8. doi: 10.1016/j.ajem.2019.158387.
[14] Chai PR, Ferro EG, Kirshenbaum JM, et al. Intentional hydroxychloroquine overdose treated with high-dose diazepam: an increasing concern in the COVID-19 pandemic. J Med Toxicol. 2020;16(3):314–320. doi: 10.1007/s13181-020-00790-8.
[15] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
[16] Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for. Syst Rev. 2016;5(1):210. doi: 10.1186/s13643-016-0384-4.
[17] Alsufyani A, King J. It's not lupus: management of a severe hydroxychloroquine poisoning in the era of medication shortages. Clin Toxicol. 2018;56(10):984–985. doi: 10.1080/15563650.2018.1506610.
[18] Berkel MV, Taylor A. A rare case of hydroxychloroquine toxicity successfully treated with intralipid emulsion therapy. Crit Care Med. 2018;46(1):431–431. doi: 10.1097/01.ccm.0000528903.23911.aa.
[19] Cole JB, Stellpflug SJ, Smith SW. Refractory hypotension and "ventricular fibrillation" with large U waves after overdose. JAMA Intern Med. 2016;176(7):1007–1009. doi: 10.1001/jamainternmed.2016.2065.
[20] Holvoet W, van Soest K, Havenith T, et al. Bail-out extracorporeal membrane oxygenation for hydroxychloroquine intoxication: a warning for COVID-19 health-care givers. Acta Cardiol. 2021;76(2):200–203. doi: 10.1080/00015385.2020.1802903.
[21] Hurley WT, Hanlon P. Lipid emulsion as an antidote at the Washington Poison Center; use in carbamazepine, flecanide, hydroxychloroquine, bupivacaine, and bupropion. Clin Toxicol. 2009;47(7):729–730. doi: 10.1080/15563650903076924.
[22] McBeth PB, Missirlis PI, Brar H, et al. Novel therapies for myocardial irritability following extreme hydroxychloroquine toxicity. Case Rep Emerg Med. 2015;2015:692948. doi: 10.1155/2015/692948.
[23] Murphy LR, Maskell KF, Kmiecik KJ, et al. Intravenous lipid emulsion use for severe hydroxychloroquine toxicity. Am J Ther. 2018;25(2):e273–e275. doi: 10.1097/MJT.0000000000000451.
[24] Ndukwu I, Ghahramani M. Hydroxychloroquine overdose presenting as acquired QT interval prolongation and torsade de pointes. J Am Coll Cardiol. 2017;69(11):2340. doi: 10.1016/S0735-1097(17)35729-7.
[25] Noda K, Akioka S, Kubo H, et al. Detoxification with intravenous lipid emulsion for fatal hydroxychloroquine poisoning. Mod Rheumatol. 2021;31(3):772–774. doi: 10.1080/14397595.2020.1812869.
[26] Onsia G, Bots S. Nearly fatal hydroxychloroquine overdose successfully treated with midazolam, propofol, sodium bicarbonate, norepinephrine, and intravenous lipid emulsion. Case Rep Emerg Med. 2021;2021:8876256. doi: 10.1155/2021/8876256.
[27] Rush K, Jenets V, Spaeder M. Phenobarbital as a substitute for diazepam in the treatment of hydroxychloroquine toxicity. Crit Care Med. 2019;47(1):465–465. doi: 10.1097/01.ccm.0000551721.15923.fb.
[28] Suen K, Harding A. Fatality in a pediatric patient following massive ingestion of hydroxychloroquine despite ECMO. North American Congress of Clinical Toxicology (NACCT). Clin Toxicol. 2023;61(Suppl 2):1–186. doi: 10.1080/15563650.2023.223383.
[29] Ten Broeke R, Mestrom E, Woo L, et al. Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication. Neth J Med. 2016;74(5):210–214.
[30] Wong O, Chan Y, Lam S, et al. Clinical experience in the use of intravenous lipid emulsion in hydroxychloroquine and chloroquine overdose with refractory shock. Hong Kong J Emerg Med. 2011;18(4):243–248. doi: 10.1177/102490791101800410.
[31] Ying DD, Wong K. Renal replacement therapy to correct refractory hypokalemia from hydroxychloroquine toxicity. Am J Respir Crit Care Med. 2023;207(1):A3491–A3491. doi: 10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A3491.
[32] Zambratto J, Nogar J, Bag MA, et al. Avoiding rebound hyperkalemia: treatment of severe hydroxychloroquine toxicity with continuous renal replacement therapy during a diazepam shortage. J Med Toxicol. 2023;19(2):75–76. doi: 10.1007/s13181-023-00930-w.
[33] Stellpflug SJ, Floan AJ, Lee SC, et al. Hydroxychloroquine overdose treated successfully with intravenous fat emulsion. Clin Toxicol. 2013;51(7):652–652. doi: 10.3109/15563650.2013.817658.
[34] Park KE, Lee SH, Bae SI, et al. Chloroquine inhibits vasodilation induced by ATP-sensitive potassium channels in isolated rat aorta. Gen Physiol Biophys. 2023;42(3):297–306. doi: 10.4149/gpb_2023008.
[35] Lee SH, Ok SH, Ahn SH, et al. Lipid emulsion inhibits the cardiac toxicity caused by chloroquine via inhibition of reactive oxygen species production. Korean J Anesthesiol. 2023;76(4):368–382. doi: 10.4097/kja.22572.
[36] Jamaty C, Bailey B, Larocque A, et al. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010;48(1):1–27. doi: 10.3109/15563650903544124.
[37] Yanturali S, Aksay E, Demir OF, et al. Massive hydroxychloroquine overdose. Acta Anaesthesiol Scand. 2004;48(3):379–381. doi: 10.1111/j.0001-5172.2004.0302.x.
[38] Radke JB, Kingery JM, Maakestad J, et al. Diagnostic pitfalls and laboratory test interference after hydroxychloroquine intoxication: a case report. Toxicol Rep. 2019;6:1040–1046. doi: 10.1016/j.toxrep.2019.10.006.
[39] Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. Am J Emerg Med. 2001;19(5):420–424. doi: 10.1053/ajem.2001.25774.
[40] Gunja N, Roberts D, McCoubrie D, et al. Survival after massive hydroxychloroquine overdose. Anaesth Intensive Care. 2009;37(1):130–133. PMID: 19157361. doi: 10.1177/0310057X0903700112.
[41] Appendix: calculated log P, log D, and pKa. In: Beale JM, Block JH, editors. Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry. 12th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2011.
[42] De Baerdemaeker K, Foxton E, Wood DM, et al. Intravenous lipid emulsion interference in coagulation testing: an ex vivo analysis. Clin Toxicol. 2024;62(7):441–445. doi: 10.1080/15563650.2024.2370324.
[43] Mullins ME. Lipid emulsion in the poisoned patient—a few answers, but more questions remain. Clin Toxicol (Phila). 2023;61(8):565–566. doi: 10.1080/15563650.2023.2254489.