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Chloroquine Use in Critically Ill Covid-19 Patients: An Ongoing Debate.

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Abstract
Severe COVID-19 related complications are difficult to manage and associated with high mortality and morbidity. The fact that chloroquine is one of the drugs being considered as a possible therapy in the management of COVID-19 is good news in developing countries where this drug is cheap, available, and relatively safe with ample experience in its use as an antimalarial drug. Severe COVID-19 disease often requires critical care, and this special population of patients require special considerations such as polypharmacy, specialist nursing care, and have unique physiology and pharmacology. Good knowledge of important issues associated with the use of chloroquine will aid the rational and efficacious use of this drug in critically ill COVID-19 positive patients. This mini mechanistic review sort to explore important issues associated with chloroquine administration that may be clinically relevant for successful critical care of COVID-19 related complications. Chloroquine has been demonstrated to have antiviral activity, anti-inflammatory activity and serve as a zinc ionophore. The role of zinc in immune homeostasis has been demonstrated as well. The issues raised may include cardiac complications, glycaemic control, pharmacogenomics, the effect on the central nervous system and eye care. Although pieces of evidence presented in this review may be weak, the issues raised may be worth considering in the rational and efficacious use of chloroquine as a potential COVID-19 therapy for severe disease.
Keywords: *Chloroquine, Covid-19, Critical Illness.*

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I. Introduction

Mortality and morbidity from severe Covid-19 related disease have been on the rise worldwide ever since the outbreak in December 2019.The virus ishighly contagious, which is responsible for the worldwide spread seen within a short period.As of October 6th, 2020, there have been about 35.6 million reported cases globally and 1,046,153 deaths from over 188 countries.The rate of spread of this respiratory virus, lack of cure and the economic consequences of managing this pandemic has heralded an ambitious search for effective treatment to manage the disease and reduce the duration of asymptomatic carriage of the virus to limit community transmission. Chloroquine,a veteran antimalarial drug is one of the candidate drugs in various stages of clinical trials worldwide, at least 80 of these trials may involve chloroquine(1,2). This information about its likely therapeutic efficacy is more beneficial to low- and middle-income countries (LMICs), because the drug is affordable, available and relatively safe for treating common diseases such as malaria, amoebiasis, cancer and certain inflammatory conditions(3,4). There isvery comprehensive experience in the use of these drug in the tropics.

An estimated 5 % to 10 % of Covid-19 positive patients require critical care and mechanical ventilation, in another study 14.2 % required critical care while 12.2 % received invasive mechanical ventilation(5,6).Critically ill patients are a special population of patients with peculiar considerations such as polypharmacy, specialist nursing care, and have unique physiology and pharmacology. Conversely, a good knowledge of the important interactions of chloroquine relevant to critical care will minimize the occurrence of medical error in off-label use, aid the prediction of adverse events with precision in clinical trials and also aid appropriate planning for the management of such events.This mechanisticreview highlights the interactions of chloroquine that is relevant and may be considered inthe critical care of complicated COVID-19 positive patients.

II. Methods

A literature review was performed using PubMed and Google Scholar to identify relevant articles published in the English language from 2005 to 2020. Search items include SARS-COV, SARS-COV2,

Covid19, and Chloroquine in combination with treatment, pharmacology and pharmacogenomics. In addition to RCTs, the authors included case reports, case series, and review articles. The authors independently reviewed the titles and abstracts for inclusion. Additional relevant articles were identified from the review of citations referenced.

ROLE OF CHLOROQUINE IN TREATMENT OF COVID-19

Chloroquine, a 4-aminoquinoline derivative, still been used in some parts of Africa and South America as an antimalarial drug was discovered to be a possible therapy in the treatment of coronavirus infections during the SARS outbreak and is now being considered in the management of the Covid-19 disease (7). The antiviral effect is exerted via several mechanisms viz: reducing endocytosis of virus by stabilizing the lysosomes, inhibiting the viral replication, inducing the production of non-infectious particles by inhibition of glycosylation of the glycoproteins, and exerts anti-inflammatory effects by inhibiting the release of proinflammatory cytokines, especially tumour necrosis factor-alpha which may ameliorate the immune reaction seen with viral infections (8,9).Additionally, chloroquine has characteristic of a zinc ionophore and specifically targets this trace element to intracellular lysosomes(9,10). Zinc status has been tightly associated with risk factors for severe COVID-19 infection including ageing, immune deficiency, obesity, diabetes, and atherosclerosis (11).Zinc cations, especially in combination with zinc ionophore pyrithione, were shown to inhibit SARS-coronavirus RNA polymerase (RNA dependent RNA polymerase, RdRp) activity by decreasing its replication (11). This information on zinc has generated interest in this trace element as part of therapy for COVID-19 infection. Researchers in LMICs should pay more attention to chloroquine and zinc for clinical trials in addition to other measures and efforts already in place. Better and properly powered randomized clinical trials should be considered(2). Chloroquine is relatively safe at therapeutic doses, adverse reactions are encountered more often either in overdose or administering therapeutic doses rapidly (4).

CHLOROQUINE AND CARDIAC COMPLICATIONS.

Cardiac side effects of chloroquine are rare but can be severe and irreversible if it occurs.Aetiology of cardiac manifestations may include direct viral myocardial injury, hypoxia, hypotension, enhanced inflammatory status or drug toxicity (12). A study of fatal outcomes of COVID-19 infection revealed myocardial injury as significantly associated with cardiac dysfunction and arrhythmia (13). The cardiac complications in chloroquine use maybe because it prolongs the QT interval(12).In a particular study of patients who used chloroquine between 3 to 35 days, 85 % developed conduction disorder, 22 % developed ventricular hypertrophy, 9.4 % developed hypokinesia, 26.8 % developed heart failure, 3.9 % developed pulmonary artery hypertension while 7.1 % had valvular dysfunction (14,15). Furthermore, 44.9 % of patients reported recovery with reversal of cardiac pathology having withdrawn from treatment, while 12.9 % had irreversible cardiac damage (14,15). Pregnancy may be a risk factor for developing cardiac complications in COVID-19 infection (16). Although, there is the paucity of data in the tropics regarding cardiac complications of chloroquine despite years of use as an antimalarial drug, aggressive treatment and monitoring with echocardiography and electrocardiography may be considered for patients at high risk of myocardial injury and to consider withdrawing chloroquine treatment in patients with cardiac manifestations. Additionally, several drugs such as macrolides, antiulcer drugs and antiarrhythmic drugs used in critical care may prolong QT interval thus increasing the risk of cardiac complications when co-administered with chloroquine, as such there should be caution in drug selection.

CHLOROQUINE AND GLYCAEMIC CONTROL

Chloroquine has been shown to lower blood glucose level and can cause hypoglycemia in chloroquine toxicity (17). This anti-diabetic mechanism may involve a decrease in insulin clearance and degradation rates and an increase in the secretion of C-peptide(4). In a study, the long-term effect of chloroquine use (6days to 6 months) in rats caused a decrease in serum glucose, insulin, calcium, potassium and protein levels, while the glucagon level increased.Acute short-term use resulted in an improvement in glucose tolerance following an oral glucose tolerance test in rats (18). Another study later revealed this can be translated to humans, hence, in India, hydroxychloroquine (achloroquine analogue) is approved for management of diabetes mellitus(19). Additionally, co-administration of metformin and chloroquine resulted in fatal toxicity in mice, this may not be significant since toxicity in mice may not automatically translate to humans (20). Glycemic control is an integral aspect of critical care because it affects outcome, as such, the COVID-19 positive patients with severe disease managed on chloroquine therapy should have a serial serum glucose monitoring in addition to the serial monitoring of electrolytes. In cases of comorbid diabetes mellitus where there maybe an increased risk of mortality, caution should be taken in using chloroquine as it increases mortality, also there may be a need to adjust the dose of antidiabetic agents whether insulin or oral antidiabetic drugs.

CHLOROQUINE AND PHARMACOGENOMICS

Chloroquine is mainly metabolized via CYP2C8 enzymes into its active metabolites, polymorphism of this cytochrome enzyme may determine the way patients respond to chloroquine treatment and also determine the extent of adverse events(21). In Africa, an estimated 1-4 % poor metabolizer of CYP2C8 enzymes exist in the population translating into several million. Thus, administration of chloroquine to this group may result in an increased incidence of adverse reactions (21). Additionally, ritonavir, an antiretroviral drug also being investigated as a candidate drug for COVID-19 treatment is a potent inhibitor of CYP2C8 enzymes, as such should probably not be administered in combination with chloroquine (21).

Chloroquine is an established inhibitor of CYP2D6 enzyme in humans, this information is important since about 25 % of clinical drugs are metabolized via this enzyme system (22,23).The effect may be modest compare to other potent inhibitors of CYP2D6 enzyme, nonetheless, it suggests a potential for drug-drug interactions when chloroquine is co-administered with other drugs such as analgesics such as opioids, antiarrhythmics, beta-adrenergic blockers and some anaesthetic agents that are substrates for this enzyme(22,24). Additionally, pharmacogenomics may explain inter-individual variability in response to chloroquine therapy (23). The clinical significance of such an interaction in critical care will depend on the therapeutic index of any drug involved as such management strategy should include monitoring of CYP2D6 genotype more comprehensively and should consider external factors for an appropriate prediction of CYP2D6 metabolizing capacity of patients with severe COVID-19 disease(24).

CHLOROQUINE AND THE CENTRAL NERVOUS SYSTEM

Chloroquine may be a potential neuroprotective agent which may be mediated via complex mechanisms.At the dose of 5mg/kg, it significantly increased seizure threshold in rats with pentylenetetrazol-induced seizure(25–27). Although these effects in rats may not necessarily translate to humans, there could be interaction with other drugs that act on the central nervous system such as sedatives and anti-seizure drugs used in the ICU. Theoretically, there may be a need for dose adjustment where chloroquine is used. Other studies demonstrated an increasing tendency to seizure in the elderly, epileptic and systemic lupus erythematosus(SLE) patients(4). Additionally, chloroquine or its analogue can cause marked neuromyopathy characterized by slowly progressive muscular weakness, which is worse in long-term use and the elderly even at standard doses.This is of concern in critically ill patients because of the risk of developing ICU acquired muscle weakness(4)resulting in difficult weaning from mechanical ventilation.

Several other case reports have associated chloroquine with agitation, aggressiveness, confusion, personality changes, loss of memory, psychosis and depression both at a therapeutic dose and overdose (4,28–31). This should ordinarily be a source of concern because the incidence of agitation is between 50 – 70 %, while 80 % of ventilated patients may suffer from delirium, it is, however, hard to generalize these because there is the paucity of data from Africa regarding these findings since another study showed that chloroquine, as well as other antimalarial, may not significantly increase the risk of psychosis in the general population(32,33).Critically ill patients being treated with chloroquine would benefit from a minimum of serial nervous system examination for early identification of adverse effects and may require dose adjustment when concomitantly administered with drugs that may increase the risk of psychosis.

CHLOROQUINE, COVID-19, AND THE EYES.

Eyecare is an important aspect of managing a critically ill patient. Generally, critically ill patients are at increased risk of ocular damage from corneal scarring, partial to permanent visual loss as a result of corneal abrasion, conjunctivitis, endophthalmitis,chemosis, exposure and microbial keratitis(34). The mechanism involved includespoor venous return and edematous state, reduced or absent blinking or reduced or absent tearing often exacerbated by high oxygen flows through ill-fitting masks or nasal cannula and fans used in ICU(34). Prone positioning in ICU as a management strategy in ARDS can further expose the patient to developing ischemic optic neuropathy and acute glaucoma(34).Evidence from china revealed that about a third of COVID-19 positive patients with severe disease had ocular manifestations such as increased secretions, chemosis, epiphora, and conjunctival hyperemia.It is, however, difficult to ascribe these manifestations to the virus since the authors admitted they did not rule out pre-existing ocular disease and it is not clear if the ocular manifestations are complications of caring for the critically ill patient as initially described in the previous paragraph.Nevertheless, this may increase the risk of developing chloroquine- associated adverse effects on the eyes(5). Chloroquine can cause two main types of adverse effects on the eyes: keratopathy and retinopathy, which can result in vision loss and microbial keratopathy which could be a focus for sepsis (4). Therapeutic dose chloroquine is generally safe; however, increased toxicity may occur even at this dose in critically ill patients due to the multiplier effect of other risks associated with either the virus itselfor sedation, paralysis or loss of consciousness seen in critically ill patients. It is, therefore, necessary to ensure proper eye care in severely ill COVID-19 patient being managed with chloroquine therapy in the ICU. Pre-existing ocular diseases should be recognized and documented for ethical reasons. Even though some feel chloroquine and COVID-19 related eye

signs are overhyped, critically ill patients with severe ARDS may require prone positioning to optimize oxygenation, paralysis or sedation for patient to tolerate intubation and mechanical ventilation, these are recognized risk factors that could precipitate ocular manifestation (34,35).

LIMITATIONS

Pieces of evidencepresented in this review may be weak and lack consistency because of possible selection and publication bias. Further studies and in-depth reviews with an emphasis on the issues raised to demonstrate whether they are clinically relevant will be required.

III. Conclusion

Chloroquine is an important candidate drug in low resource countries for the treatment of COVID-19 both as an off-label drug and in clinical trials since it has not been established as an effective therapy. The vast experience with its use in Africa and other low resource settings is birthed with a paucity of data concerning its use and adverse effects, nevertheless, great caution should be exercised because possible adverse effects associated with its use is well established and documented. This caution is particularly important in the critical care of severe COVID-19 cases to improve outcome.

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