Received Date: 28 May 2020
Accepted Date: 6 July 2020
Published Date: 14 July 2020

Practique Clinique et Investigation

Role of Chloroquine and Hydroxychloroquine in the Treatment of COVID-19

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INTRODUCTION

Chloroquine was discovered in 1934 by Hans Andersag (German scientist) while he was working for the Bayer Pharmaceutical Company, and this drug was initially called (Resochin) [1,2]. In 1945, the World Health Organization (WHO) recommended the use of chloroquine in the treatment of malaria, which was a deadly disease in many cases [3,4]. Both chloroquine and hydroxychloroquine (safer analogue) with the chemical formula shown in Figure 1 are currently considered to be important drugs listed as anti-malaria agents according to the WHO, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) [5,6]. Moreover, hydroxychloroquine is presently widely used to treat autoimmune diseases such as lupus and rheumatoid arthritis [7,8]. Both medications are considered safe drugs whose side effects are generally mild. However, their use must be subjected to strict rules, and self-treatment (without direct medical supervision) is not recommended due to their narrow therapeutic index [9,10].

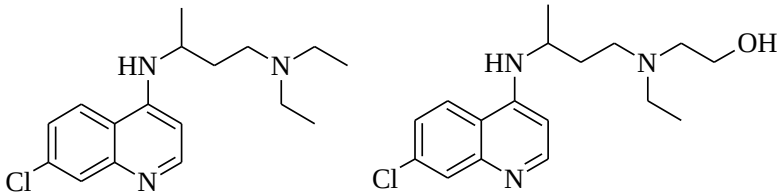

Figure 1: Chemical structure of chloroquine and hydroxychloroquine.

ANTI-VIRAL ACTIVITY

In vitro antiviral activity of chloroquine has been identified since the late sixties as scientists were able to inhibit the growth of many different viruses by chloroquine and hydroxychloroquine [11]. More recently, the ability of both drugs to inhibit the growth of viruses from the corona family (2004), as well as later the Ebola virus were identified [12-15]. Subsequently, several in vivo experiments in mice were conducted to test the efficacy in vitro of both drugs to inhibit the growth of viruses. The experiments suggested that the drugs were effective against both corona (OC43) [16,17] and influenza (A H5N1), but lack activity against the Ebola virus [18,19]. In addition, many clinical studies were conducted to test the ability of both chloroquine and hydroxychloroquine to inhibit the growth of viruses [20,21]. These clinical studies indicate that no severe viral infection can be treated with chloroquine or hydroxychloroquine although a modest effect of chloroquine in treating human infection with chronic hepatitis C was reported [22].

Citation: Nisreen H Meiqal, Role of Chloroquine and Hydroxychloroquine in the Treatment of COVID-19. Prac Clin Invest 3(S1): 5-8.

ANTIVIRAL ACTIVITY AGAINST THE EMERGING CORONA VIRUS (SARS-COV2)

After the emergence of the COVID-19 pandemic, many drugs and chemical compounds that inhibited viruses in the past were tested against SARS-CoV2 virus. Initially, *in vitro* investigation of chloroquine's ability to inhibit the emerging corona virus (SARS-CoV2) was reported in China (February 2020) indicating high activity [23,24]. These investigations were followed by several in vitro and clinical studies that aimed to demonstrate the ability of chloroquine and hydroxychloroquine to inhibit SARS-CoV2 virus in China and some other countries [25-27].

Based on the results of these studies, the following statements can be concluded:

1. Chloroquine and hydroxychloroquine exhibit good in vitro efficacy (anti SARS-CoV2) [25-27].
2. More in vivo studies are required to determine the pharmacokinetic properties of Chloroquine and hydroxychloroquine as possible anti SARS-CoV2 drugs.
3. A variety of clinical studies are registered in various countries to test chloroquine and hydroxychloroquine ability to inhibit the emerging corona virus (SARS-CoV2) [28-31]. Accordingly, some specialized institutions in some countries and international consortia started to include chloroquine and hydroxychloroquine as part of their medical protocol to treat COVID19 patients. However, this initiation is regarded problematic due to the lack of proof of efficacy as well as fear of unexpected clinical side effects [32,33].
4. Recently, clinical studies (multinational registry analysis) of the use of chloroquine and hydroxychloroquine with or without a macrolide (a class of natural products that consist of a large macrocyclic lactone ring with one or more deoxy sugars attached) for treatment of COVID-19 was reported based on COVID 19 patients hospitalized in different countries. The achieved results indicated lack of evidence of benefit of both medications to effectively treat COVID 19 patients. In addition, there was an associated increase of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19 [33-35].
5. Based on the findings listed in point (4), the FDA warned against using of chloroquine and hydroxychloroquine outside the medical framework, the WHO suspended their clinical trials for safety reasons, and their use as part of the treatment protocols were later stopped by the French government.

CONCLUSION

Chloroquine or its analogues appeared a hope for humanity in the treatment of the COVID-19 disease. Chloroquine is cheap and safe (if used under medical supervision), and early results of *in vitro* studies were promising. However, this initial achievement requires further investigation to verify the suitability and safety of their use. Currently, WHO does not recommend any specific antiretroviral drugs against SARS-CoV2, citing the lack of sufficient evidence to recommend any specific treatment that includes chloroquine or its analogues? To determine the efficacy of chloroquine or its analogues to treat COVID 19, it will be necessary to provide more financial support for the continuation of clinical trials.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the technical support and valuable suggestions obtained from Ms. Amira Abdul Gbaj (Novelien Zone, Tripoli, Libya).

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