AMJ Australasian Medical Journal [AMJ 2020;13(12):304-309]

Antimalarial use in managing COVID-19 in the context of Glucose-6-Phosphate-Dehydrogenase G6PD deficiency: A mini review

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REVIEW

Please cite this paper as: Al-Ani AHHDA, Othman N, Al-Ani SHH. Antimalarial use in managing COVID-19 in the context of Glucose-6-Phosphate-Dehydrogenase G6PD deficiency: A mini review. AMJ 2020;13(12):304–309.
https://doi.org/10.35841/1836-1935.13.12.304-309

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ABSTRACT

Background
The use of certain medications in G6PD deficient patients can trigger an oxidative stress which can lead to haemolytic anaemia. Recently, in a few countries, Chloroquine and Hydroxychloroquine; drugs that are indicated for prevention and treating malaria have been used in the management of COVID-19 patients. Evidently, the use of chloroquine and hydroxychloroquine can cause negative impact to the haemolytic status of COVID-19 G6PD deficient patients.

Aims
The aim of this mini review was to provide an overview of the use of antimalarial agents in the management of COVID-19 G6PD deficient patients.

Methods
We conducted a review of the literature that has examined the use of antimalarial agents in the management of COVID-19 G6PD deficient patients.

Results
Chloroquine and hydroxychloroquine have been found to exhibits an antiviral activity against several viral infection including human coronaviruses. Many countries have implemented the use of Chloroquine and Hydroxychloroquine in managing COVID-19 patients. However, according to published case reports, the use of Chloroquine and hydroxychloroquine have been shown to worsen the haemolytic status in G6PD deficient patients.

Conclusion
COVID-19 infection can trigger severe acute haemolytic crisis in G6PD-deficient patients which can be worsened by chloroquine and hydroxychloroquine. Thus, physicians should be aware to this possible adverse event particularly in countries with high prevalence of G6PD deficiency.

Key Words
COVID-19, G6PD deficiency, chloroquine, hydroxychloroquine

What this study adds:

1. What is known about this subject?
Since declaring COVID-19 as a pandemic, many therapeutic agents have been used in the management of this disease. These include the Antimalarial agents (Chloroquine and Hydroxychloroquine).

2. What new information is offered in this study?
Acute haemolytic events can be triggered by COVID-19 infection and worsened by the use of antimalarial therapy in G6PD deficient patients.

3. What are the implications for research, policy, or practice?
Healthcare-professionals should be aware of this possible adverse-event and should practice caution when using such agents, particularly in countries with high prevalence of G6PD deficiency.

Background

Glucose-6-phosphate dehydrogenase G6PD is a cytoplasmic enzymes that are found in all cells of the human body.[1] It plays an important role in preventing the cellular damage as it catalyses the rate-limiting reaction and the first step of the pentose phosphate pathway PPP in which NADPH is produced as a result of oxidization of glucose-6-phosphate into 6-phosphogluconolacton.[2-4] NADPH is essential to reduce glutathione which is important in protecting the cells from oxidative damage.[5,6] The red blood cells (RBCs) are vulnerable to the formation of reactive oxygen species which is also known as free radicle.[2,3]

Glucose-6-phosphate-dehydrogenase G6PD deficiency

G6PD enzyme is encoded by the Gd gene which is located at the long arm of X chromosomes. It follows X-linked inheritance meaning that the deficient phenotype is fully manifested in males while in females G6PD deficiency will vary due to X-chromosome inactivation.[3,7] However, most G6PD deficient patients are asymptomatic unless being exposed to oxidative stress.[1] Medicines, consumption of fava beans, infection, and stressful physical exercise can trigger oxidative stress resulting in the clinical manifestation of G6PD deficiency which includes acute haemolytic anaemia, neonatal jaundice, favism, and chronic nonspherocytic haemolytic anaemia (Figure 1).[8]

Antiviral activity of chloroquine and hydroxychloroquine

Chloroquine, a well-known antimalarial drug has been shown to have an antiviral activity against several viral infections.[9-12] It exhibits its antiviral activity either directly or indirectly.[13] Since chloroquine is a small, amphiphilic, lipophilic weakly basic substance, it can easily penetrate the cell membrane raising its PH resulting in blockage of viral activity.[13,14] In addition, chloroquine can interferes with cell membrane receptors' structure and prevent the attachment or combination of virus to these receptor. It has been shown that, chloroquine can act indirectly by inhibiting the production and release of tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) i.e., inhibiting the inflammatory mediators responsible for complications of several viral diseases (Figure 2).[9,15-17]

Coronavirus disease 2019 COVID-19, hydroxychloroquine therapy, and G6PD deficiency

COVID-19 is a public health emergency that became of international concern. On the 11th of March 2020, COVID-19 was declared as a pandemic by the World Health Organization (WHO). COVID-19 is a highly infectious disease, and associated with clinical symptoms that include fever, dry cough, sore throat, headache, conjunctivitis, gastrointestinal issues, fatigue, myalgia, and dyspnoea. Currently there is a lack for a specific treatment to be used to treat COVID-19 infection.[18] However, several studies have suggested chloroquine and hydroxychloroquine to have an in-vitro potential inhibitory action against COVID-19.[19,20] In addition, several studies favourable clinical efficacy and virologic benefit (i.e., reducing the viral load) when using chloroquine phosphate and hydroxychloroquine in COVID-19 patients.[21-23]

However, a previous experimental study showed that the viral gene expression are higher in G6PD deficit cells i.e., G6PD deficient patient's cells are more vulnerable to human corona virus 229E.[12] A recently published case report indicated that COVID-19 infection could result in severe acute haemolytic crisis in G6PD deficient patient.[24] In addition, antimalarial agents particularly chloroquine has a potential oxidative properties that can reduce glutathione levels which may results in severe haemolysis in G6PD deficient patients and should be avoided in such patients.[3]

In the context of COVID-19 infection, treating G6PD deficient patients can be challenging especially when considering chloroquine and its derivative hydroxychloroquine due to the fact that the patient will be under two sources of oxidative stress i.e., the infection and medication which can trigger a haemolytic event in G6PD deficient patients.[25,26] A case of a 68-year-old male G6PD deficient patient who developed a severe haemolytic crisis due to COVID-19 infection, and the administration of hydroxychloroquine shown to prolong and worsen the haemolytic state in their patient. According to the retrospective analysis of the case, COVID-19 infection was found to be the trigger for the haemolysis and the administration of hydroxychloroquine was associated with worsening blood parameters in this patient.[24] This was also seen in a case report by Kuipers et al.[27] for a 58-year-old male patient who was diagnosed with COVID-19 infection and chloroquine treatment was initiated. However, their

patient's haemoglobin level dropped from 11.4g/dL to 8.9g/dL within 12 hours after chloroquine administration. Further investigations showed that the patient has G6PD deficiency.[27] Similarly, Maillart reported a case of COVID-19 65-year-old male patient who experienced an acute haemolysis after hydroxychloroquine administration as the patient's haemoglobin level dropped from 13.3g/dL to 11.8g/dL within 24 hours after hydroxychloroquine administration, which resulted in admission to the intensive care unit due to acute renal failure resulted from acute haemolysis due to hydroxychloroquine use in the context of G6PD deficiency.[28] Similarly, a 72-year-old male has experienced a rapid dropped in the haemoglobin level after 48 hours of hydroxychloroquine therapy initiation. The patient appeared to have G6PD deficiency.[29]

G6PD deficiency is more prevalent in the tropical Africa and Arabian Peninsula.[30] This can explain why most of the reported patients were from African background (Table 1). With regards to the time of haemolytic events, it happened after treatment initiation (Chloroquine/ Hydroxychloroquine) in most of reported cases.[27,28] In contrast, it started before the initiation of hydroxychloroquine in one case. However, it worsened after the use of hydroxychloroquine.[24] This can indicate that both COVID-19 infection and G6PD deficiency are responsible of haemolytic events in COVID-19 G6PD deficient patient i.e., chloroquine/hydroxychloroquine associated severe haemolytic events can develops more rapidly and prominently when the antioxidant reserves (NADPH) are depleted due to the severe inflammatory status associated with COVID-19 infection.[27,31]

Conclusion

Since declaring COVID-19 as a pandemic disease, it is still threatening millions of lives, particularly immunocompromised patients and patient with comorbidities. The fast-spreading of the disease globally requires emergency therapy. Many countries have implemented the use of chloroquine and hydroxychloroquine in the management of COVID-19. However, several reports demonstrated that COVID-19 infection can trigger severe acute haemolytic crisis in G6PD-deficient patients which can be worsened by chloroquine and hydroxychloroquine. Thus, health professionals should be aware to this possible adverse event particularly in countries with high prevalence of G6PD deficiency.

References

1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64–74.
2. Antwi-Baffour S, Adjei JK, Forson PO, et al. Comorbidity of glucose-6-phosphate dehydrogenase deficiency and sickle cell disease exert significant effect on RBC indices. Anemia. 2019;2019.
3. Richardson SR, O'Malley GF. Glucose 6 phosphate dehydrogenase (G6PD) deficiency. 2017.
4. Arese P, Gallo V, Pantaleo A, et al. Life and death of glucose-6-phosphate dehydrogenase (G6PD) deficient erythrocytes–role of redox stress and band 3 modifications. Transfus Med Hemother. 2012;39(5):328–34.
5. Efferth T, Schwarzl S, Smith J, et al. Role of glucose-6-phosphate dehydrogenase for oxidative stress and apoptosis. Cell Death Differ. 2006;13(3):527–8.
6. Cunningham AD, Hwang S, Mochly-Rosen D. Glucose-6-phosphate dehydrogenase deficiency and the need for a novel treatment to prevent kernicterus. Clin Perinatol. 2016;43(2):341–54.
7. Hwang S, Mruk K, Rahighi S, et al. Correcting glucose-6-phosphate dehydrogenase deficiency with a small-molecule activator. Nat Commun. 2018;9(1):1–12.
8. Ong KIC, Kosugi H, Thoeun S, et al. Systematic review of the clinical manifestations of glucose-6-phosphate dehydrogenase deficiency in the Greater Mekong Subregion: implications for malaria elimination and beyond. BMJ Glob Health. 2017;2(3).
9. Keyaerts E, Li S, Vijgen L, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother. 2009;53(8):3416–21.
10. Kouroumalis E, Koskinas J. Treatment of chronic active hepatitis B (CAH B) with chloroquine: a preliminary report. Ann Acad Med Singap. 1986;15(2):149–52.
11. Singh AK, Sidhu GS, Friedman RM, et al. Mechanism of enhancement of the antiviral action of interferon against herpes simplex virus-1 by chloroquine. J Interferon Cytokine Res. 1996;16(9):725–31.
12. Wu YH, Tseng CP, Cheng ML, et al. Glucose-6-phosphate dehydrogenase deficiency enhances human coronavirus 229E infection. J Infect Dis. 2008;197(6):812–6.
13. Al-Noaemi MC, Hammoodi AH. COVID-19 and Hydroxychloroquine relationship in the past, present, and future. Pharma Innov J. 2020;9(4):248–52.
14. Ashfaq UA, Javed T, Rehman S, et al. Lysosomotropic agents as HCV entry inhibitors. Virol J. 2011;8(1):1–6.
15. Savarino A, Boelaert JR, Cassone A, et al. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003;3(11):722–7.
16. Farias KJS, Machado PRL, Muniz JAPC, et al. Antiviral

activity of chloroquine against dengue virus type 2 replication in Aotus monkeys. Viral Immunol. 2015;28(3):161–9.
17. Biguetti C, Marrelli MT, Brotto M. Primum non nocere–Are chloroquine and hydroxychloroquine safe prophylactic/treatment options for SARS-CoV-2 (covid-19)? Rev Saude Publica. 2020;54:68.
18. Şimşek Yavuz S, Ünal S. Antiviral treatment of COVID-19. Turk J Med Sci. 2020;50(SI-1):611–9.
19. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
20. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732–9.
21. Gao J, Hu S. Update on use of chloroquine/ hydroxychloroquine to treat coronavirus disease 2019 (COVID-19). Biosci trends. 2020.
22. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020.
23. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949.
24. Beauverd Y, Adam Y, Assouline B, et al. COVID-19 infection and treatment with hydroxychloroquine cause severe haemolysis crisis in a patient with glucose-6-phosphate dehydrogenase deficiency. Eur J Haematol. 2020.
25. Burka ER, WEAVER III Z, MARKS PA. Clinical spectrum of hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med. 1966;64(4):817–25.
26. Francis RO, Jhang JS, Pham HP, et al. Glucose-6-phosphate dehydrogenase deficiency in transfusion medicine: the unknown risks. Vox Sang. 2013;105(4):271–82.
27. Kuipers MT, van Zwieten R, Heijmans J, et al. G6PD deficiency-associated hemolysis and methemoglobinemia in a COVID-19 patient treated with chloroquine. Am J hematol. 2020.
28. Maillart E, Leemans S, Van Noten H, et al. A case report of serious haemolysis in a glucose-6-phosphate dehydrogenase-deficient COVID-19 patient receiving hydroxychloroquine. Infect Dis. 2020:1–3.
29. De Franceschi L, Costa E, Dima F, et al. Acute hemolysis by hydroxycloroquine was observed in G6PD-deficient patient with severe COVD-19 related lung injury. Eur J Intern Med. 2020;77:136-7.
30. Howes RE, Piel FB, Patil AP, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. PLoS Med. 2012;9(11):e1001339.
31. Jain SK, Parsanathan R, Levine SN, et al. The potential link between inherited G6PD deficiency, oxidative stress, and vitamin D deficiency and the racial inequities in mortality associated with COVID-19. Free Radic Biol Med. 2020;161:84–91.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

Figure 1: Role of Glucose-6-phosphate dehydrogenase G6PD in the pentose phosphate pathway PPP

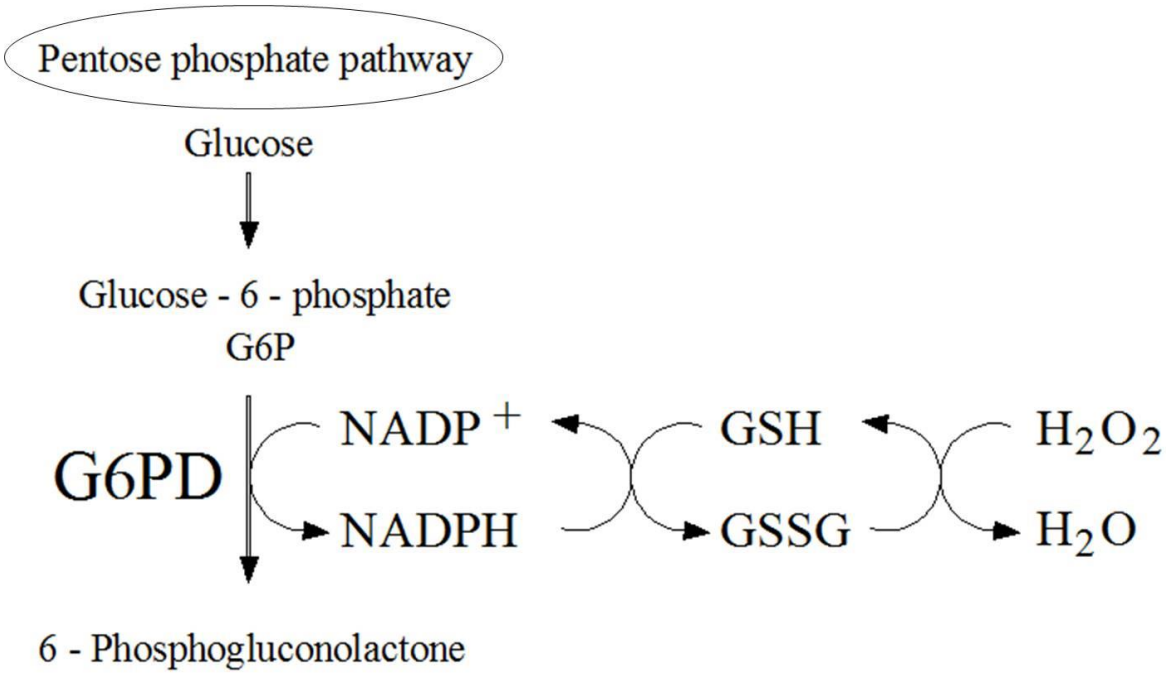

Figure 2: Mechanisms of chloroquine/hydroxychloroquine antiviral activity

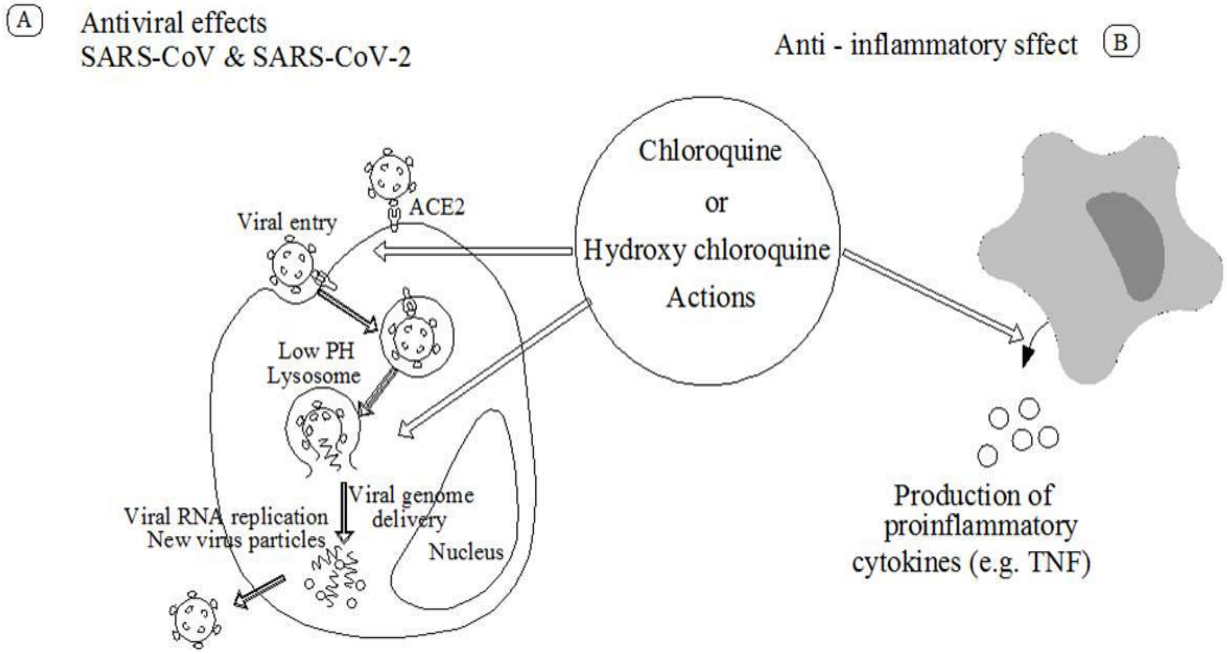

Table 1: Summary of COVID-19 G6PD deficient patients treated with Chloroquine or Hydroxychloroquine

Study	Age (years)	Gender	Race	Comorbidities	Antimalarial used	Haemolysis started after medication used	Complications
Beauverd et al., 2020[24]	68	Male	· African	· Type II diabetes mellitus · Hypertension · Chronic renal insufficiency	· Hydroxychloroquine 600mg for 1 day	· No, but blood parameters worsened after initiating Hydroxychloroquine therapy.	· Worsening hemolysis
Kuipers et al., 2020[27]	58	Male	· African-Caribbean	· Type II diabetes mellitus	· Chloroquine 600mg for 1 day	· Yes	· Hemolysis
Mailmart et al., 2020[28]	65	Male	· African	· Type II diabetes mellitus · Hypertension	· Hydroxychloroquine 400mg BID for 1 day then 200mg BID day 2-5	· Yes	· Acute hemolysis · Acute renal failure due to hemolysis
De Franceschi et al., 2020[29]	72	Male	· Caucasian	· Ischemic cardiomyopathy	· Hydroxychloroquine for 2 days	· Yes	· Hemolysis