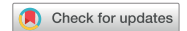



CASE REPORT



A case report of serious haemolysis in a glucose-6-phosphate dehydrogenase-deficient COVID-19 patient receiving hydroxychloroquine*

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ABSTRACT

While the COVID-19 epidemic occurred since December 2019, as of end April 2020, no treatment has been validated or invalidated by accurate clinical trials. Use of hydroxychloroquine has been popularised on mass media and put forward as a valid treatment option without strong evidence of efficacy. Hydroxychloroquine (HCQ) has its own side effects, some of which are very serious like acute haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. Side effects may be worse than the disease itself. Belgian national treatment guidelines recommend the use of HCQ in mild to severe COVID-19 disease. As opinions, politics, media and beliefs are governing COVID-19 therapy, performance of randomised controlled blinded clinical trials became difficult. Results of sound clinical trials are eagerly awaited. We report a case of acute haemolysis leading to admission in intensive care unit and renal failure in a patient with uncovered G6PD deficiency.



KEYWORDS

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Introduction

Treatment for SARS-CoV2 disease (COVID-19) is still ill defined more than four months after the recognition of the epidemic in China [1]. Some experts advocate for the use of chloroquine or hydroxychloroquine (HCQ) [2]. Azithromycin was reported to have an additional effect to hasten viral clearance. In the meantime, those non randomised, uncontrolled, open label 'studies', performed over a very small number of patients, were counteracted by a similarly underpowered study [3]. With about 10% mortality rate and an overwhelming attack rate, COVID-19 disease is so frightening that even non evidence-based medical decisions have been taken. Without waiting for the results of randomised controlled trials (RCT), broad use of HCQ is advertised [4]. In Belgium, the national consensus guidelines recommend the use of hydroxychloroquine for mild and severe COVID-19 cases [5]. As chloroquine is not available, we resort to hydroxychloroquine. In our institution, all admitted patients requiring oxygen support and having symptoms for less than ten days are put on hydroxychloroquine 400 mg BID day 1 and 200 mg BID day 2–5 in addition to azithromycin 500 mg day 1 and 250 mg day 2–5. Hydroxychloroquine is an old drug, with well-characterised side effects, mainly used in rheumatic diseases. Some side effects are acquired after chronic cumulative exposure like retinopathy or cardiomyopathy, others are acute like haemolytic anaemia in those deficient in glucose-6-phosphate dehydrogenase (G6PD) activity, rhythm perturbations due to QT prolongation, idiosyncratic like liver toxicity, hypoglycaemia, epilepsy, drug-drug interactions, among others [6]. While we are using hydroxychloroquine off-label, awaiting firm data confirming, or not, its efficacy, we already observed serious side effects that highlight the need for careful monitoring.

From 15 March 2020 to 27 April 239 patients have been put on hydroxychloroquine plus azithromycin in our institution. We report one case of acute severe haemolysis related to hydroxychloroquine in a patient of African origin.

Case report

A 65-year-old man originated from Cameroon was admitted for hypoxaemia, mid-March 2020. Past medical history revealed hypertension and type 2 diabetes. There was no history of drug-induced haemolysis. Baseline biology showed: Hb 13.3 g/dl, MCV 98 fl, platelet $144 \times 10^3/\mu\text{l}$, WBC $3.57 \times 10^3/\mu\text{l}$, absolute lymphocyte

count: $1.27 \times 10^3/\mu\text{l}$, CRP 71.3 mg/l, DFG (CKD-EPI): $>90 \text{ mL/min/1.73m}^2$, Hb A1c: 10.3%, total bilirubin 0.9 mg/dl, Glucose: 247 mg/dL, blood gas: pH 7.43, pO₂ 58, pCO₂ 38 mm Hg. Chest CT scan showed ground glass lesions disseminated in five lobes with 40–50% of parenchyma involved. SARS CoV-2 PCR on a naso-pharyngeal swab was positive. Hydroxychloroquine and azithromycin were started on the admission day. The next day, haemoglobin dropped at 11.8 g/dl. On day 2, the patient's condition worsened and he was admitted in the ICU. On day 5, haptoglobin was below detection level, total bilirubin: 4.4 mg/dl, LDH: 1743, DFG (CKD-EPI) [mL/min/1.73m²]: 18. Hydroxychloroquine was stopped on day five. Glucose-6-phosphate-dehydrogenase activity was below 0.2 U/g of haemoglobin. Lactate levels were normal during all ICU stay excluding hypo-perfusion as a cause for renal failure. The patient was intubated for 7 days and underwent Continuous Venovenous Haemodialysis and Filtration (CVVHDF). He received multiple blood transfusions. After 18 days in the ICU, he was transferred to a conventional unit. Biology showed HB: 7.2 g/dl, platelets $557 \times 10^3/\mu\text{l}$, WBC $8.7 \times 10^3/\mu\text{l}$, total lymphocyte $2.43 \times 10^3/\mu\text{l}$, CRP 74.3 mg/l, DFG (CKD-EPI) [mL/min/1.73m²]: 6, LDH 605, haptoglobin became detectable again on day 15 after hydroxychloroquine administration. ICU stay conclusion was ARDS due to COVID-19, acute haemolysis due to G6PD deficiency and acute renal failure due to haemolysis. Hydroxychloroquine level was still at 93 µg/L 30 days after its administration.

Discussion

Our patient received hydroxychloroquine according to national guidelines which have been validated internally. Lack of experience in using that specific drug and confusion between COVID-19 deterioration and HCQ toxicity caused a delay in the recognition of the side effect and drug interruption.

Acute haemolysis is a known side effect of hydroxychloroquine in G6PD deficient patients [7]. In our institution, G6PD activity testing is available as a routine test during working hours. Guidelines do not recommend routine G6PD testing before HCQ prescription [8,9]. However, another case report also warns about serious haemolysis in a G6PD deficient COVID-19 patient [10]. The prevalence of G6PD deficiency among non-Hispanic African-American was 9.5% in a series of members of U.S. Armed Forces [11]. Due to particular taxing situations, non-validated therapeutics are used, putting our

patients at risk of serious side effects. Clinicians should not rush to use unproven therapy which may be more deleterious than the disease itself. Clinical trials should be/can be hastened to provide evidence-based therapy even in this crisis time [12]. Should HCQ becomes the mainstay of COVID-19 treatment, faster access to G6PD activity testing should be offered in population where G6PD deficiency is prevalent using point of care tests.

Conclusion

Non validated therapeutics are used to face the SARS-CoV-2 epidemic, among which hydroxychloroquine. Many national guidelines have recommended HCQ use while awaiting adequate randomised controlled clinical trials. We describe a case of serious haemolysis due to hydroxychloroquine use in an uncovered glucose-6-phosphate dehydrogenase deficient COVID-19 patient. This side effect should be considered in case of haemolysis particularly in patients of African ascendance. Biological signs of haemolysis should be followed during COVID-19 disease and in particular when HCQ is used. Patients should be warned about potential side effects of HCQ and if diagnosed with G6PD deficiency, informed about drugs to avoid in the future.

Ethical approval

The patient has given written consent to the inclusion of material pertaining to himself, he acknowledged that he cannot be identified *via* the paper; and we have fully anonymized the case report.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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