



ORIGINAL RESEARCH

Severe Hypoglycemia in a Nondiabetic Old Woman Treated with a Single Oral Dose of Hydroxychloroquine for Covid-19

Daive Moro^{1*}, Giacomo Gastaldi², Dina Zekry¹ and Christine Serratrice¹

¹Division of Internal Medicine for the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Switzerland

²Division of Endocrinology, Diabetology, Hypertension and Nutrition, Geneva University Hospitals, Switzerland



*Corresponding author: Daive Moro, Division of Internal Medicine for the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Hôpital des Trois Chêne, 1256 Thonex, Switzerland

Introduction

During the Covid-19 pandemic, local therapeutic guidelines recommended to treat every hospitalized Covid-19 patient with hydroxychloroquine (HCQ) or ritonavir/lopinavir, after consent and in absence of contra-indications. Chloroquine (CQ) (Nivaquine®) and its derivative hydroxychloroquine (HCQ) (Plaquenil®) are two antimalarial of the amino-4-quinoline class which are usually used to treat chronic inflammatory conditions such as rheumatoid polyarthritis or lupus [1]. Due to their action against macrophage activation, they have been proposed in infectious diseases, specially Q fever or Ebola infection [2].

Case Description

We report the case of a 75-year-old woman, admitted to the emergency geriatrics unit because of asthenia, non-bloody watery diarrhoea, vomitus and flu-like symptoms, started two days earlier. She had also rhinorrhoea without dyspnea, abdominal or chest pain. As far as she knew, she had no contact with Covid-19 infected individuals.

She had no relevant medical history and no known allergies. She was non-smoker and had no history of alcohol consumption. She is married, the couple has a son and she is autonomous for Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). The patient has no cognitive or thymic disorders. The

Nutrition Risk Screening (NRS-2002) is 1 point. The Functional Independence Measure (FIM) is 115/126 points. The Comprehensive assessment method score (CAM) is negative for confusional state. The Cumulative Illness Rating Scale for Geriatrics score (CIRS-G) is 1 point.

She was usually treated with Calcium-Vitamin D-25-OH and dry extracts of Ginkgo biloba.

On clinical examination, vital signs were normal with blood pressure at 116/75 mmHg, heart rate at 81/minute, regular, body temperature at 36.6 °C, oxygen saturation at 100% in ambient air, and respiratory rate at 12/minute. The patient was asthenic and presented a dry cough. No acute respiratory distress syndrome (ARDS) criteria were observed. Clinical examination was normal except mildly increased noises in all four abdominal quadrants.

Laboratory tests showed a normal white-cell count with lymphopenia at 0.66 g/l, the C-reactive protein level was 8.8 mg/L, sodium was 125 mmol/l and fast glycemia was 4.2 mmol/l. Renal and liver functions were normal. An oropharyngeal swab for Covid-19 testing was positive. The ECG was normal, with a QT interval (QTc) at 442 msec. Chest X-ray showed a discrete bilateral reticulonodular infiltrate. No thoracic CT scan was performed, as the diagnosis of Covid-19 was clear and she had a normal pulmonary clinical exam.

In accordance with local recommendations of the

University Hospital of Geneva, Switzerland, and in absence of contraindication, a single dose of 800 mg of HCQ was given on day 2. The 800 mg single-order dose was determined based on a pharmacokinetic and pharmacodynamic (PK/PD) model which extrapolated that at this dose and ten days after the administration, the pulmonary HCQ concentration is just above the half maximal effective concentration (EC 50), and therefore sufficient for presumed efficacy against SARS-CoV-2. On one side, the aim is to minimize the side effects of the medication, especially in our geriatric population, considering its long half-life and its tendency to a strong accumulation in tissues. On the other side, with an important single dose posology, the goal is to reach more rapidly this presumed effective drug concentration in lungs against SARS-CoV2 infection compared to other protocols where HCQ is given for a longer time but starting with lower dosage as we have seen in other countries.

Nine hours after administration of HCQ, the patient was drowsy without other anomaly at the neurologic examination (Glasgow Coma Scale at 15/15). Capillary blood glucose was 1.2 mmol/L. The patient recovered after intravenous glucose infusion (Glucose 40% 10 ml). The capillary blood glucose level was then 12.5 mmol/L. Performed after this episode of severe hypoglycemia, dosage of plasma insulin was 14.3 mU/L [N: 2.6-24.9 mU/L], C-Peptide was 1142 [N: 370-1470] and morning basal cortisol was 420 nmol/l (N > 350 nmol/L).

Based on the medical history clinical and laboratory manifestations the evaluation of the hypoglycemia confirmed that our patient had no predisposing conditions such as insulinoma, starvation, ethanol intake, oral anti-diabetic and exogenous insulin usage, liver failure or sepsis that can lead to hypoglycemia.

Discussion and Conclusion

One of the recognized side effects of HCQ is hypoglycemia. As HCQ is an acidotropic agent, when HCQ concentration is high, the intracellular alkalization leads to an inactivation of insulinase. Through this mechanism, insulin is not degraded in the lysosomal environment and an increase in the plasma concentration of insulin and the prolongation of its action is observed [3]. Due to its pharmacokinetics profile [4] with a half-life of around 50 days, local institutional recommendations were to use a single 800 mg dose of HCQ for Covid-19 as previously mentioned. Indeed, the risk of hypoglycemia seems to be related to the level of blood HCQ concentration, especially when associated with renal failure [5] which was not the case in our patient.

In conclusion, the case reported is about in-hospital severe non-diabetic hypoglycemia, a rare condition predictor of in-hospital mortality [6] with an estimated incidence around 40 per 10,000 admissions in patients over 65-years-old [7]. Mostly, non-diabetic hypoglycemia is observed in case of alcohol dependence, renal failure

and sepsis. We suggest treating physicians to pay particular attention to the eventuality of hypoglycemia in patients treated with HCQ, especially in the elderly and other vulnerable populations.

The risk of hypoglycaemia, known to occur while on HCQ therapy is much higher when the overall treatment regimen includes insulin or sulfonylurea as when the patient is suffering of diabetes mellitus. In such case glucose level should be monitored after starting HCQ treatment at least five times per day after its introduction and adapted according to blood glucose levels.

Finally, before prescribing HCQ, patients should be well informed about such side effects of HCQ as hypoglycemia. More efforts should be done to better understand the physiopathology of the homeostasis of glucose concerning patients who take HCQ. In this way, further randomized, controlled, double-blind and much larger studies about what we reported with this case report, the hypoglycemic effect of HCQ, are needed in order to better understand this aspect.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Vanden Borne BEEM, Dijkmans BAC, deRooij HH, leCes-sie S, Verweij CL (1997) Chloroquine and hydroxychloro-quine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *J Rheumatol* 24: 55-60.
2. Akpovwa H (2016) Chloroquine could be used for the treat-ment of filoviral infections and other viral infections that emerge or emerged from viruses requiring an acidic pH for infectivity. *Cell Biochem Funct* 34: 191-196.
3. Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Ada-mu BA, et al. (2020) Potential effect of hydroxychloroquine in diabetes mellitus: A systematic review on preclinical and clinical trial studies. *Journal of Diabetes Research* 2020: 5214751.
4. Schrezenmeier E, Dorner T (2020) Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheu-matology. *Nat Rev Rheumatol* 16: 155-166.
5. El-Solia A, Al-Otaibi K, Ai-Hwiesh AK (2018) Hydroxy-chloroquine-Induced hypoglycaemia in non-diabetic re-nal patient on peritoneal dialysis. *BMJ Case Rep* 2018: bcr2017223639.
6. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M (1998) Hypoglycemia in hospitalized nondiabetic older pa-tients. *J Am Geriatr Soc* 46: 978-982.
7. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, et al. (2012) Hypoglycemia in Non-Diabetic In-Pa-tients: Clinical or Criminal? *PLoS One* 7: e40384.