DOI：10.6314/JIMT.202106_32(3).06 內科學誌 2021：32：195-198

Hydroxychloroquine Induced Severe Prolonged Hypoglycemia in An Elderly Woman

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Abstract

I report a severe prolonged hypoglycemia side effect of the often-used drug hydroxychloroquine in a non-diabetic elderly woman with undifferentiated connective tissue disease. Although the mechanism of lowering blood glucose levels has not been clarified yet, but severe and prolong hypoglycemia need to be keep in mind. Therefore, in clinical practice, we must be careful when prescribe this drug for patients and check glucose levels in the initial phase. Education on hypoglycemia self-management may also be performed. (J Intern Med Taiwan 2021; 32: 195-198)

Key Words: Hydroxychloroquine, Hypoglycemia, Undifferentiated connective tissue disease, Drug induce hypoglycemia

Introduction

Hydroxychloroquine (HCQ) is commonly used drugs in the treatment of rheumatic disease, systemic lupus erythematosus (SLE) and other undifferentiated connective tissue disease. In previous reports, hydroxychloroquine also could diminish the risk of diabetes mellitus and cardiovascular disease[1]. In a recent published open label non-randomized clinical trial, HCQ significantly reduce and disappear viral load in Coronavirus disease 2019 (COVID-19) patients and the effect of HCQ is reinforced by azithromycin[2]. In many treatment guidelines of COVID-19 pneumonia, HCQ became the first choosing medicine. Comparing to retinopathy and prolong QTc, hypoglycemia is a rare side effect of HCQ[3]. However, severe hypoglycemia had been reported in non-diabetic patient with lupus nephritis on peritoneal dialysis and rheumatologic disease[4]. The long elimination half-life (~ 40 days) require us to bear the side effect in mind[5]. Here, I report a case of undifferentiated connective tissue disease induced anemia and thrombocytopenia, who got severe hypoglycemia after 4 weeks of HCQ therapy.

Case presentation

This 82 years old woman with previous medical history of dementia, and undifferentiated connective tissue disease was sent to our emergency department by nursing home staff because of drowsy consciousness found for about 12 hours. She was diagnosed with other undifferentiated connective tissue disease induced thrombocytopenia and nor-

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mocytic normochromic anemia about 5 week ago, so she began received hydroxychloroquine (400mg/day) and methylprednisolone (12 mg/day) therapy. Before arriving emergency department, the blood glucose was 32 mg/dl measured at ambulance then 20 mg/dl at emergency department. Consciousness regained and her symptoms disappeared after 80 ml of 50% dextrose parenterally infused.

Normal physical examination without neurologic focal sign was found after regaining consciousness. In the laboratory evaluation, hemoglobin A1c value was 5.8%, hemoglobin was 11.0 g/dL, hematocrit level was 33.1%, leukocyte count was 9,000/KL, platelet count was 141,000/KL and growth hormone was 4.050 ng/ml. Serum albumin, liver enzymes, urea, creatinine, adrenal gland function test, and thyroid functions tests were within normal limits. During glycaemia 42 mg/dl, the serum level of insulin was 69.34 uIU/ml (normal range: 2.6~24.9 uIU/ml), beta-hydroxybutyrate was 0.3 mmol/L (normal range: 0~0.6 mmol/L) and C-peptide was 20.62 ng/ml (normal range 0.81~3.85 ng/ml). Computer tomography of abdomen and endoscope ultrasound revealed normal pancreas.

Because of recurrent hypoglycemia during follow-up, intravenous infusion of 10% dextrose parenterally was infused (60cc/hour). During the initial 2 days, the blood glucose was measured every 2 hours, but blood glucose got low to less than 60 mg/dl if stopping 50% dextrose infused more than 2 hours, even10% dextrose infusion kept.

Three days later, the 50% dextrose was discontinued but 10% dextrose infusion kept because her capillary glucose levels remained around 100- 150 mg/dL during her regularly frequent blood glucose measuring. Then, one week later, the 10% dextrose was quitted because her blood glucose levels greater than 200 mg/dL for 5 times of sequential follow-

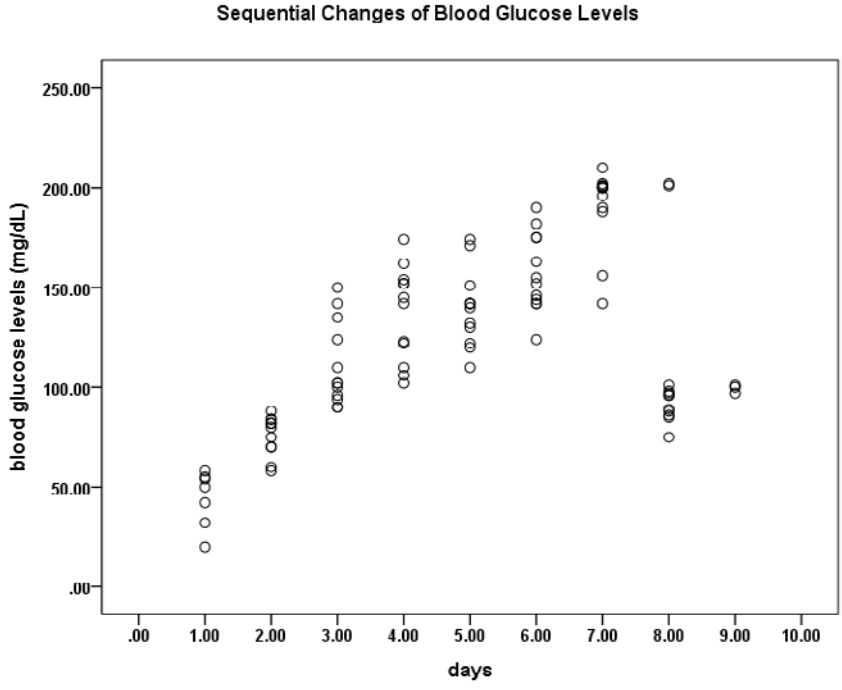

Figure 1. Day 1-2: Glucose intravenous infusion were 80 ml of 50% dextrose every 4 hours and continuing 60ml/hour of 10% dextrose.
Day 3-7: Glucose intravenous infusion was only continuing 60ml/hour of 10% dextrose.
Day 8: All glucose intravenous infusion was quitted.

up blood glucose measuring. Figure 1 revealed the sequential changes of blood glucose levels during admission.

After discharge, continuous glucose monitoring was performed at nursing home. Several episodes of lower blood glucose levels to below 70 mg/dl were still revealed even on high glucose diet. Until 1 month later, no lower blood glucose levels were measured and with an average of 103 mg/dl on normal glucose diet.

Two months later, she was re-admitted for 72-hour fasting evaluation. The test was stopped at the 72nd h because of no blood glucose level less than 55 mg/dL. Insulin and C-peptide levels within normal limits were also revealed at the end of the test (2.9 uIU/ml and 0.83 ng/ml, respectively). After discharge, negative insulin autoantibody was noted by laboratory investigation at medical center.

Discussion

In the differential diagnosis of hypoglycemia in a patient without diabetes mellitus, in addition to insulinoma, drug induced hypoglycemia is also an important risk factor. Hydroxychloroquine (HCQ) induced hypoglycemic effect is rare (less than 3%), but its long elimination half-life (~40 days) may induce long-term hypoglycemia[6]. This side effect may appear at 2 weeks and persisted for 6 months[7]. In this case, from clinical and laboratory data there was no predisposing disorder which could induce hypoglycemia such as oral anti-diabetic drug or exogenous insulin usage, septic shock, liver failure, renal failure or endocrine dysfunction. Otherwise, the patient didn't have postprandial hypoglycemia, compatible with nesidioblastosis. During hypoglycemia status, the c-peptide and insulin were still high, so insulin autoimmune antibody or insulinoma should be ruled out. The possibility of an insulinoma was also ruled out with computer tomography of abdomen and endoscope ultra-sound. The hypoglycemia was also completely subsided after quitted HCQ for one month. The insulin antibody was also negative.

Quinine could lower blood glucose was found 95 years ago[8]. Phillips et al first published quinidine induced severe hypoglycemia[9]. HCQ could inhibit of intracellular degradation of insulin and hepatocyte gluconeogenesis[10,11]. It may increase insulin secretion in pancreatic islet cells to induce hyperinsulinemia hypoglycemia in patient with diabetes mellitus and benign dose dependent[12,13]. HCQ used in patients with diabetes and pre-diabetes to lower blood glucose were also presented. HCQ could decreased insulin requirements in refractory type 2 diabetes by an average of 30%[3]. In Unübol et. Al's case report, the prediabetes patient with rheumatoid arthritis got HCQ induced hypoglycemia, then got marked hyperglycemic course after quitted HCQ. This also suggested that the patient had prediabetes or diabetes previously, which went undiagnosed because suboptimal glucose regulation was obtained with HCQ treatment[12]. Therefore, being an antidiabetic agent was advised at previous investigating article[14]. In a prospective study, which enrolled 250 T2DM patients with uncontrolled glycemia on multiple oral hypoglycemic agents, HCQ effectively improved glycemic control in these patients after add-on treatment with 400 mg once daily for 48 weeks[15] Comparing to non-HCQ user, patients who with SLE or rheumatoid arthritis but without diabetes used HCQ 200-400 mg/day had lower fasting plasm glucose as well as lower logHOMA-IR[1]. In conclusion, this presented case with undifferentiated connective tissue disease but not diabetes mellitus in treatment with HCQ got prolong and severe hypoglycemia. HCQ can reduce blood glucose levels and the side effect should be born in mind. In clinical practice, we must check glucose levels in the initial phase of HCQ usage. Rheumatologists should be alert to the possibility of hypoglycemia due to HCQ as well as endocrinologists must list this drug in differen-

tial diagnosis and studying hypoglycemia in patient without diabetes.

Disclosure statement

No conflict of interest state.

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一位年長婦女在服用羥氯喹後引發長時間嚴重低血糖

謝靜蓉

寶建醫療社團法人寶建醫院　內科部
美和科技大學護理學系

摘　要

本個案報告為一位罹患未分化型結締組織疾病但無糖尿病病史的老婦人，在服用常用藥物羥氯喹5週後發生長時間且嚴重低血糖的罕見個案。雖然羥氯喹會降低血糖的機轉目前並不十分了解，但是其會發生嚴重且持續很長時間的低血糖須讓我們牢記於心。因此在臨床處方羥氯喹時，臨床醫師需於治療初期檢測病患血糖及執行低血糖衛教。