Case Report

Hydroxychloroquine-Induced Hypoglycemia in a Non-Diabetic Patient with Chronic Kidney Disease and Rheumatoid Arthritis

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ABSTRACT: Hydroxychloroquine (HCQ) is an immunomodulatory medication commonly used to treat several autoimmune diseases. Due to its tendency to change insulin metabolism by increasing production and reducing clearance, HCQ can cause hypoglycemia in patients with or without diabetes, albeit this is rare. There is documented evidence of HCQ-induced hypoglycemia in the literature. However, none to our knowledge has reported this adverse effect in a patient with chronic kidney disease not undergoing dialysis. We describe the case of an 81-year-old woman who went to the emergency room for care after experiencing abrupt dizziness and unconsciousness. Pertinent history includes four prior episodes of hypoglycemia after the recent initiation of HCQ for rheumatoid arthritis. Fasting glucose was <40 mg/dL on presentation. Given the appearance of symptoms after the initiation of the medication and the absence of symptoms with normal glucose upon discontinuation, it was concluded that HCQ was the likely culprit for the recurrent episodes of hypoglycemia. Physicians should be aware of this rare but possible adverse effect of HCQ, especially in older patients and patients with chronic kidney disease. Prompt elimination of the medication can reduce the risk of some of the devastating consequences of hypoglycemia.

KEYWORDS: *Hydroxychloroquine, hypoglycemia, adverse effect, rheumatoid arthritis, chronic kidney disease.*

Introduction

Hydroxychloroquine (HCQ) is an aminoquinoline antimalarial agent commonly used to treat several autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [1].

More recently, HCQ has been used in combination with azithromycin and low-molecular-weight heparin in the treatment of patients hospitalized with COVID-19 [2].

Although rare, hypoglycemia is a well-documented adverse effect of HCQ [3].

The mechanism underlying low blood glucose (BG) is thought to be related to HCQ-induced increases in insulin secretion and inhibition of clearance [4].

This effect is more likely to occur in patients with chronic kidney disease (CKD), given the reduced renal clearance at baseline, which produces more pronounced symptoms due to lower BG than average [4,5].

Cases regarding HCQ-induced hypoglycemia are well-documented in the literature; however, none to our knowledge has commented on this adverse effect in a patient with CKD not on dialysis.

In patients with recurrent hypoglycemic episodes, we suggest a thorough review of the medication list to identify a drug as a potential cause.

We present a rare case of HCQ-induced hypoglycemia in a non-diabetic patient with CKD undergoing treatment for RA.

Case Report

An 81-year-old female presented to the emergency department (ED) accompanied by her husband with sudden onset dizziness, fatigue, and loss of consciousness (LOC).

Per the patient's partner, she was lying in bed when she suddenly endorsed dizziness, fatigue, and subsequent LOC.

These symptoms are associated with tremors, nausea, diaphoresis, and irritability.

The patient has notably had five prior hospitalizations for hypoglycemia within the past two months, for which several workups were negative.

She reported a previous 72-hour fast and adrenocorticotropic hormone (ACTH) stimulation test (normal response >18-20mcg/dL; baseline cortisol 7.1mcg/dL →24.1mcg/dL after 30 minutes →26.1mcg/dL after 60 minutes) that were normal.

Upon presentation to the ED, she was tachycardic (110 beats/min).

Other vital signs were within normal range.

On general appearance, she was in moderate distress, intermittently responding to questions.

Heart sounds were present in all valvular areas and lungs were noted without any abnormality.

Her medical history included depression, gastroesophageal reflux disease, insomnia, and RA adequately treated with HCQ 200mg twice daily.

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In the ED, laboratory values revealed hemoglobin 11.2g/dL (Normal=N 12-16), white blood cells 4300/mm^3 (N 4500-11000), platelets 145,032/mm^3 (N 150,000-400,000/mm^3), creatinine 1.8mg/dL (N 0.6-1.2mg/dL), BG 30mg/dL (N 70-139), and phosphorus 5.8mg/dL (N 2.4-4.7).

Other lab results, such as coagulation profile and blood gas, were within range.

She was admitted to the intensive care unit on a custom 20% dextrose infusion with subsequent normalization of BG.

A computed tomography scan of the abdomen/pelvis was performed to rule out a mass in the pancreas, which was negative.

The patient was transferred to the medical floor, where the endocrine team was consulted.

She underwent a 72-hour fast (Table 1) and an ACTH stimulation test that were both negative.

A mixed meal tolerance test showed no abnormal findings.

Upon further questioning of the patient, she started HCQ 6 months before her first episode of hypoglycemia.

The patient was instructed to stop HCQ and see an endocrinologist in two weeks due to concerns for medication-induced hypoglycemia.

Rheumatology was consulted, who recommended prednisone as needed for RA flares.

She was given a continuous glucose monitor (Dexcom) on discharge to a skilled nursing facility.

At her two-week follow-up, the patient endorsed intermittent dizziness and tremors with occasional LOC.

Dexcom readings recorded three episodes of hypoglycemia with the lowest BG of 48mg/dL.

She was advised to continue holding HCQ and follow up in 2 months.

At her subsequent follow-up, Dexcom recorded no events of hypoglycemia, with her lowest BG reading of 80mg/dL.

Her rheumatologist was notified, who pursued other medical options for RA.

Table 1. Serum parameters after a 72-hour fast[1]

Serum Parameters	Patient values	Normal range
Glucose (mg/dL)	65	70-139
Insulin (µU/mL)	3	2-23
C-peptide (ng/mL)	0.8	0.7-4.4
Proinsulin (pmol/L)	2.8	≤7.2
Anti-insulin receptor antibodies	Negative	None
Anti-insulin antibodies	Negative	None
Analog insulin	Negative	None

[1]Results showed normal levels of insulin, proinsulin, and C-peptide in the setting of mild hypoglycemia with a glucose of 65mg/dL. There was no evidence of analog insulin, antibodies, or anti-insulin receptor antibodies. These findings are reassuring of a normal 72-hour fast.

Discussion

HCQ is an immunomodulatory and anti-inflammatory agent commonly used to treat autoimmune and rheumatic diseases, such as SLE and RA [6].

It gained notoriety during the COVID-19 pandemic, when it was used experimentally to treat SARS-CoV-2 infection [7].

Although well tolerated, HCQ is associated with a broad range of adverse effects, including cytopenias, cardiomyopathy, allergic reactions, and skin hyperpigmentation [7,8].

Long-term use of HCQ is also associated with ocular toxicity, including corneal deposits, ciliary body dysfunction, vascular attenuation, and optic disc pallor [8,9].

A well-documented but rare adverse effect is hypoglycemia.

There have been several published cases of HCQ-associated hypoglycemia in patients with or without diabetes [3,10].

However, none to our knowledge has described such an adverse effect in a patient with concurrent CKD not on dialysis. Cansu *et al.* reported a case of HCQ-induced hypoglycemia in a nondiabetic patient without kidney disease [11].

Similarly, Yaghji *et al.* reported HCQ-induced hypoglycemia in a non-diabetic patient without any other chronic disease [12].

Before determining if hypoglycemia was medication-induced in our case, additional etiologies were first excluded.

The testing focused on a number of laboratory tests, such as the C-peptide level, insulin, and cosyntropin stimulation test.

Adrenal insufficiency was tested using the ACTH stimulation test.

To evaluate insulin-mediated hypoglycemia, on the other hand, insulin and C-peptide levels were measured as a baseline in a mixed-meal study.

Since all of these findings were normal, some of the more frequent causes of hypoglycemia were correctly ruled out.

HCQ has a complex pharmacokinetic profile predominantly due to its large volume of distribution and significantly long half-life [13].

The half-life is approximately 40-50 days; therefore, we can estimate that HCQ takes up to 36 weeks to be completely eliminated from the body, based on the rules of half-lives [13,14].

Patients with factors affecting clearance, such as liver and kidney disease, will have HCQ eliminated at a slower rate, thereby contributing to longer stints of adverse effects [15].

In our case, the patient had CKD, which may have contributed to her continued severe hypoglycemic symptoms after the medication was held in the first two weeks.

Cases of HCQ-induced hypoglycemia have reported BG between 50 and 60mg/dL on admission; however, none are as severe as in our case with a BG of 30mg/dL on admission [3-5,16].

This lower value of BG can potentially be attributed to higher levels of HCQ-inducing hypoglycemia due to inadequate clearance.

Studies on chloroquine have been used to extrapolate the suggested mechanism of hypoglycemia associated with HCQ [17].

In vitro, chloroquine enhances intracellular insulin accumulation, decreases intracellular insulin breakdown, postpones receptor recycling, and stimulates insulin-mediated glucose transport [17,18].

Additionally, a reduction in insulin resistance has been noted [17].

Since the patient's symptoms improved after stopping the medicine at the two-month follow-up, this case report contributes to the body of knowledge already available on HCQ-induced hypoglycemia.

A score of 7 on the Naranjo Adverse Drug Reaction Probability scale indicated a likely connection between hypoglycemia and HCQ (Table 2) [19].

Table 2. The Naranjo Adverse Drug Reaction Probability Scale

Question	Answer	Score
Are there previous conclusive reports on this reaction?	Yes	+1
Did the adverse event appear after the suspected drug was given?	Yes	+2
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	Yes	+1
Did the adverse reaction appear when the drug was readministered?	N/A	0
Are there alternative causes that could have caused the reaction?	No	+2
Did the reaction reappear when a placebo was given?	N/A	0
Was the drug detected in any body fluid in toxic concentrations?	N/A	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	N/A	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	N/A	0
Was the adverse event confirmed by any objective evidence?	Yes	+1
Total score		7

N/A=Not applicable.

Several other case studies have reported scores suggesting a likely association between HCQ and hypoglycemia [10,11].

Although there is no direct link between HCQ and hypoglycemia episodes, in this instance, stopping the drug was important because it was most likely the cause of her recurrent symptoms.

Given the cessation of symptoms upon stoppage of the medication in conjunction with the Naranjo scale, we can safely assume the association between HCQ and hypoglycemia, exacerbated by CKD.

Conclusion

In summary, we report a scarce adverse effect of a medication. HCQ-induced hypoglycemia is well-documented.

However, this case was unique in that symptoms of hypoglycemia were exacerbated by the underlying comorbidity of CKD in a non-dialysis patient.

Physicians should be aware of this medication-related adverse effect and stop the

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drug in patients with recurrent episodes of hypoglycemia.

After stoppage, these patients are managed with long-term follow-up.

Author Contributions

K.E wrote the original draft, contributed to conceptualization, writing, reviewing, and editing of the manuscript; The author read and approved the final version of the manuscript.

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Conflicts of interest

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Institutional Review Board

Not applicable

Consent Statement

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Data availability

All data presented in the manuscript are available from the authors upon request.

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