Severe hypoglycemia secondary to hydroxychloroquine: A case report

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BACKGROUND

- Hydroxychloroquine is an aminoquinoline antimalarial agent used to treat various autoimmune diseases. More common adverse reactions include retinopathy, blood dyscrasias, and dermatitis.[1]
- Rarely, cases of hypoglycemia have been reported with hydroxychloroquine and chloroquine, also an aminoquinoline antimalarial, occurring in less than 1% of users.[1]
- Onset of hypoglycemia in case reports has been after weeks to years of treatment .
- The mechanism by which hydroxychloroquine causes hypoglycemia is unclear, however a proposed mechanism includes impaired insulin metabolism.

CASE REPORT

- A 38-year-old Caucasian female was brought to Mercy Hospital of Buffalo Emergency Department (ED) via emergency medical services (EMS) for a witnessed seizure event.
- She had a past medical history of end-stage renal disease (ESRD) on hemodialysis (HD) secondary to polycystic kidney disease, seizure disorder, anemia of chronic disease, asthma, hypertension, mitral and tricuspid valve stenosis, and recently diagnosed systemic sclerosis.
- Pertinent home medications included levetiracetam, carvedilol, and hydroxychloroquine. The patient reported hydroxychloroquine had been initiated the day prior to admission for her recently diagnosed systemic sclerosis and reported no other recent medication changes. The patient endorsed adherence to her medications and reported that her last seizure was approximately 10 years prior (Table 1).
- Pertinent labs upon EMS arrival include an undetectable blood glucose (BG) reading x four on two separate devices.
- A repeat fingerstick BG checked on arrival and was < 40 mg/dL. An ampule of dextrose 50% was administered and repeat BG was 116 mg/dL (Table 1, Figure 1).
- Laboratory studies on arrival to the ED were significant for hyperkalemia (7.7 mmol/L) and anemia (hemoglobin 5.9 mg/dL). Thyroid function was checked and revealed an elevated Thyroid Stimulating Hormone (TSH) of 8.35 IU/mL and a normal Free T4 of 1.11 ng/dL (Table 3).
- Toxicologic studies were negative. A levetiracetam level was checked and was 16.6 mcg/mL indicating compliance which the patient endorsed (Table 4).
- Neurology was consulted and recommended outpatient follow-up and no changes to her current medication regimen.

Home Medication List
Amlodipine 10mg orally daily
Carvedilol 6.25mg orally twice daily
Famotidine 10mg orally daily
Ferric citrate 420mg orally three times daily with meals
Hydroxychloroquine 200mg orally twice daily
Levetiracetam 250mg orally twice daily
Loratadine 10mg orally daily
Albuterol MDI inhale 2 puffs every 6 hours as needed for shortness of breath

Table 1. Home medications; MDI = metered dose inhaler

CASE REPORT

Hospital Day	Blood Glucose (mg/dL)
0	< 40
0	116
1	110
2	106

Table 2. Blood glucose readings

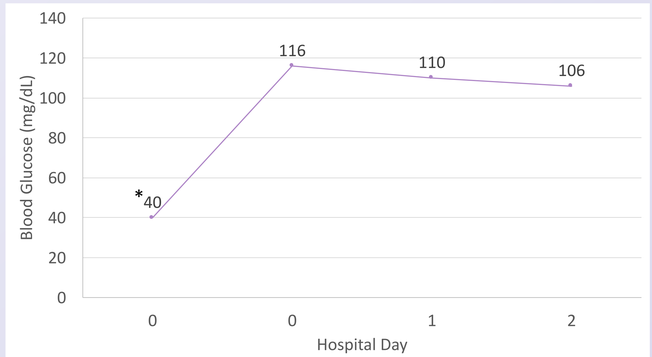

Figure 1. Blood glucose readings per hospital day; *Initial blood glucose was less than 40 mg/dL

Laboratory Test (units)	Result
Sodium (mmol/L)	137
Potassium (mmol/L)	7.7
Chloride (mmol/L)	96
Bicarbonate (mmol/L)	14
Anion Gap	27
BUN (mg/dL)	60
Creatinine (mg/dL)	9.61
TSH (IU/mL)	8.35
T4, free (ng/dL)	1.11
Leukocytes (10*3/mcL)	6.8
Hemoglobin (g/dL)	5.9
Hematocrit (%)	19.5
Platelets (10*3/mcL)	236

Table 3. Laboratory studies on hospital day 0; BUN = Blood Urea Nitrogen, TSH = Thyroid Stimulating Hormone

Pertinent Drug/Toxicological Levels	
Levetiracetam mcg/mL	16.6
Acetaminophen mcg/mL	< 10
Salicylates (mg/dL)	< 10
Ethanol (mg/dL)	< 10

Table 4. Drug/Toxicology levels on hospital day 0

Disclosure:
The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

DISCUSSION

Hydroxychloroquine, an aminoquinoline antimalarial, remains a mainstay of treatment for various inflammatory and rheumatologic diseases. Rarely, hypoglycemia has been reported with the aminoquinolines chloroquine and hydroxychloroquine. Case reports of hypoglycemia with the aminoquinolines have been documented in the literature. The first documented case of hydroxychloroquine-induced hypoglycemia in a non-diabetic patient was published in 2008 by Cansu and colleagues. They describe a case of severe hypoglycemia in an 80-year-old patient taking hydroxychloroquine for two months.[2] Recently Mardones and colleagues report a case of recurrent, unexplained hypoglycemia in a patient taking hydroxychloroquine for two years.[3] Additional case reports describe similar findings of hypoglycemia in patients taking hydroxychloroquine ranging from months to several years.[4,5]

Cases of chloroquine-induced hypoglycemia have also been documented. In a 1987 study published in the British Medical Journal demonstrated an effect of chloroquine on fasting blood glucose levels in patients with Type 2 Diabetes Mellitus. The authors proposed that chloroquine and other aminoquinolines could be utilized in the management of diabetes.[6]

The mechanism for hydroxychloroquine-induced hypoglycemia is not well understood. A proposed mechanism is an effect on insulin metabolism leading to increased insulin levels. Emami and colleagues proposed that hydroxychloroquine leads to a decrease in degradation of insulin. They demonstrated a non-competitive inhibition of insulin protease (insulinase) by hydroxychloroquine in vitro.[7]

Lysosomal hepatic accumulation is a second proposed mechanism of for decreased insulin degradation leading to hypoglycemia. Macintyre and colleagues demonstrated accumulation of chloroquine in the lysosomes of the liver due to difference in pH. This accumulation alters the pH of the lysosome, preventing degradation of insulin. The hepatic accumulation of insulin downregulates the production of insulin receptors and thus reduces insulin metabolism.[8]

Although not definitively confirmed, we propose that hydroxychloroquine was the cause of this patient's severe hypoglycemia. Our patient presented with her first seizure in 10 years which was likely caused by a decreased seizure threshold due to hypoglycemia. This patient had no history of diabetes or episodes of hypoglycemia. We propose that this patient was at increased risk of hypoglycemia due to her renal failure which is why this patient presented so soon after initiation.

In this patient, the temporal relationship of hydroxychloroquine initiation and presentation, extensive objective evidence of severe hypoglycemia, and seizure upon presentation make this a unique case. The Naranjo Adverse Drug Reaction Probability Scale indicated a probable reaction with a score of 7. [9]

CONCLUSIONS

Although rare, hypoglycemia should be monitored for in patients taking hydroxychloroquine who are at risk of developing or having signs and symptoms of hypoglycemia.
Hypoglycemia caused by hydroxychloroquine may manifest after several months to years of therapy. We describe a case of severe, rapid-onset hypoglycemia in a high-risk patient.

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