Hydroxychloroquine Associated Hyperinsulinemic Hypoglycemia

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Introduction

Hypoglycemia in the patient without diabetes mellitus is uncommon.[1] An initial evaluation of hypoglycemia begins with confirming Whipple's triad which includes: the presence of sympathoadrenal and neuroglycopenic symptoms, documented low plasma glucose concentration, and resolution of symptoms when plasma glucose is raised.[2] Hypoglycemia secondary to hydroxychloroquine previously has been documented in humans.[3,4] We describe a case of severe hyperinsulinemic hypoglycemia in a patient initiated on hydroxychloroquine therapy.

Case Report

A 66-year-old female with a complex medical history including rheumatoid arthritis and pyoderma gangrenosum, but without known history of either diabetes mellitus or exposure to glucose lowering medications, was admitted to the hospital for evaluation and management of anasarca. While hospitalized, the patient was initiated on hydroxychloroquine for management of her rheumatologic disorders. Within hours of her first dose of hydroxychloroquine, the patient developed hypoglycemia with a glucose value of 28 mg/dL on serum measurement. She was symptomatic with diaphoresis, tremors, and confusion. Her symptoms resolved with administration of dextrose.

Additional pertinent medical history included a long-standing history of chronic exogenous steroid use due to her rheumatologic disorders. At the time of this hypoglycemic event, the patient was placed on stress dose steroids (hydrocortisone 100mg IV q 8 hours). She did not have a history of prior bariatric surgery, renal insufficiency, uncontrolled hypothyroidism, or findings to suggest an infectious etiology of hypoglycemia.

Although standard hypoglycemic laboratory was not obtained with the initial hypoglycemic event, the patient had multiple additional episodes of symptomatic hypoglycemia, despite receiving stress dose steroids, at which time a standard hypoglycemic laboratory evaluation was undertaken. Diagnostic laboratory captured at the time of a recurrent hypoglycemic event was consistent with hyperinsulinemic hypoglycemia (Table 1).

In light of hyperinsulinemic hypoglycemia without known exposure to oral hypoglycemic agents, a computed tomography scan of the abdomen was obtained. This study was negative for any evident pancreatic mass and given the temporal relationship of administration of hydroxychloroquine to development of hypoglycemia, no further imaging was obtained. Due to prior case reports associating hydroxychloroquine with hypoglycemia,

Table 1. Hypoglycemic laboratory evaluation.

	Glucose	Insulin	C-peptide	Proinsulin	Hypoglycemic Screen
Reference Ranges for Endogenous Hyperinsulinemia	< 55 mg/dL	≥ 3.0 U/mL	≥ 0.2 nmol/L	≥ 5 pmol/L	Negative
Patient Values	53 mg/dL	102.9 U/mL	6.0 nmol/L	330 pmol/L	Negative

this medication was discontinued prior to any additional doses being administered. Hypoglycemia persistently recurred over an approximately ten-hour period following the first dose of hydroxychloroquine, then it resolved without recurrence, confirming hydroxychloroquine as the causative agent. The patient was followed in the hospital setting for an additional four days without recurrence of hypoglycemia. In addition, she was seen in ambulatory follow-up within one month of discharge without recurrent events.

Discussion

Hypoglycemia is a rare, but well recognized, adverse effect of treatment with anti-malarial agents including hydroxychloroquine and chloroquine.[3] Hypoglycemia secondary to hydroxychloroquine has been documented previously in the medical literature, both in patients with diabetes on stable doses of glucose lowering drugs as well as patients without a prior history of diabetes and on no hypoglycemic agents.[3,6]

The mechanism of hydroxychloroquine-induced hyperinsulinemic hypoglycemia has been inferred from studies on chloroquine, which is structurally similar. In the streptozocin-treated type 1 diabetic rat model, chloroquine led to higher levels of insulin with concomitant drops in blood glucose.[9] Additionally, a second study has shown an increase in the level of plasma immunoreactive insulin in rats treated with chloroquine.[10] This is thought to be due to enhanced insulin secretion from beta cells,[10] as well as inhibition of insulin degradation by chloroquine.[11]

Animal studies have shown that hydroxychloroquine increases insulin levels in diabetic rats, thereby decreasing serum glucose levels. This increase in insulin also has been found to be concentration-dependent to the amount of hydroxychloroquine administered.[12]

The glycemic effects of hydroxychloroquine in humans have been well-described in several clinical studies evaluating its use in treatment and prevention of diabetes mellitus. It improves glycemic control in individuals with diabetes with and without autoimmune diseases.[13,14] It significantly decreased glycated hemoglobin and fasting glucose in patients with type 2 diabetes mellitus that previously had been non-responsive to sulfonylureas and other medications for diabetes.[13-15] Hydroxychloroquine has been associated with a decreased risk of development of diabetes mellitus in patients with rheumatologic disorders.[16-18]

Conclusion

We described a case of severe and persistent hyperinsulinemic hypoglycemia with initiation of hydroxychloroquine in a patient without diabetes mellitus. This case report adds to the sparse literature surrounding this important clinical topic. Based on animal data, the cause of hydroxychloroquine-induced hyperinsulinemic hypoglycemia is thought to occur via

two different mechanisms: enhanced insulin secretion from beta cells as well as inhibition of insulin degradation. The proposed mechanisms behind hydroxychloroquine-induced hypoglycemia are consistent with the laboratory results of our patient. Although the literature supporting the role of hydroxychloroquine as an agent associated with hyperinsulinemic hypoglycemia is limited, there is mounting evidence of hydroxychloroquine's role in diabetes prevention in patients' with rheumatologic disorders. Healthcare providers and patients should we aware of the potential for modulation of glycemic status with this class of medications.

References

[1] Nirantharakumar K, Marshall T, Hodson J, et al. Hypoglycemia in non-diabetic in-patients: clinical or criminal? PLoS One 2012; 7(7):e40384**.** PMID:22768352.

[1] Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94(3):709-728. PMID: 19088155.

[2] Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. J Rheumatol 1999; 26(1): 195-196. PMID: 9918262.

[3] Powrie JK, Smith GD, Shoajee-Moraddie F, Sönksen PH, Jones RH. Mode of action of chloroquine in patients with non-insuline-dependent diabetes mellitus. Am J Physiol 1991; 260(6 Pt.1):E897-E904. PMID: 2058666.

[4] Cansu DU, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford) 2008; 47(3):378-379. PMID: 18222983.

[5] Kang L, Mikuls TR, O'Dell JR. Hydroxychloroquine: A diabetic drug in disguise? BMJ Case Rep 2009. Epub 2009 Mar 2. PMID: 21686697.

[6] Unübol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol 2011; 17(1):46-47. PMID: 21169846.

[7] Garcia-Webb P, Bonser AM. Insulin binding and degradation in isolated hepatocytes from streptozotocin injected rats. Biochem Biophys Res Commun 1985; 128(2):487-493. PMID: 3888217.

[8] Asamoah KA, Robb DA, Furman BL. Chronic chloroquine treatment enhances insulin release in rats. Diabetes Res Clin Pract 1990; 9(3):273-278. PMID: 2146103.

[9] Kobayashi M, Iwasaki M, Shigeta Y. Receptor mediated insulin degradation decreased by chloroquine in isolated rat adipocytes. J Biochem 1980; 88(1):39-44. PMID: 6997286.

[10] Emami J, Gerstein HC, Pasutto FM, Jamali F. Insulin-sparing effect of hydroxychloroquine in diabetic rats is concentration dependent. Can J Physiol Pharmacol 1999; 77(2):118-123. PMID: 10535702.

[11] Penn SK, Kao AH, Schott LL, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 2010; 37(6):1136-1142. PMID: 20436082.

[12] Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med 1990; 112(9):678-681. PMID: 2110430.

[13] Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2

diabetes mellitus who are refractory to sulfonylureas-a randomized trial. Diabetes Res Clin Pract 2002; 55(3):209-219. PMID: 11850097.

[14] Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA 2007; 298(2):187-193. PMID: 17622600.

[15] Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA 2011; 305(24):2525-2531. PMID: 21693740.

[16] Bili A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol 2011; 17(3):115-120. PMID: 21441823.

Keywords: hydroxychloroquine, hyper-insulinemia, hypoglycemia