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Case Report

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Hypoglycemia due to hydroxychloroquine, an uncommon association but to keep in mind, case report and review of literature

Abstract

Case presentation: Female patient, 44 years old, in treatment for an Indeterminate Connective Tissue Disease with Deflazacort and Hydroxychloroquine. It began with a compatible clinical presentation of hypoglycemia objectified between 30 and 60 mg/dl. Fasting test rules out the biochemical possibility of insulinoma, and with no findings that suggest obvious disease that is responsible for hypoglycemia. It is attributed to hydroxychloroquine, which is suspended. Soon, the clinical presentation of hypoglycemia disappears and the patient remains asymptomatic.

Discussion: The study of hypoglycemia in a context of a non-diabetic patient is always a challenge. A correct medical history and physical examination can give clues about the origin of hypoglycemia. Within the differential diagnosis are the uses of medications that cause hypoglycemia. One of them, hydroxychloroquine, widely used for the treatment of rheumatic diseases, has been described as causing hypoglycemia, although it is a rare occurrence with this drug, but it is well documented in the literature. We review the cases described in the literature and the mechanisms that may explain hydroxychloroquine hypoglycemia.

Keywords: hypoglycemia, glucose metabolism, hydroxychloroquine

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Patricio Salman Mardones,[1] Iván Quevedo Langenegger,[1] Macarena Arias Thormann,[1] Carlos Stehr Gesche,[1] Andrea Bancalari Selman[2]

[1]Department of Internal Medicine, Concepcion University, Chile
[2]Regional Clinical Hospital of Concepcion, Chile

Correspondence: Patricio Salman Mardones, Assistant professor of the Faculty of Medicine of Concepcion University, Department of Internal Medicine, Faculty of Medicine, Chacabuco with Janequeo, 4th floor, Concepcion University, Chile, Tel (56-41) 2204921, Email psalman@udec.cl

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Abbreviations: HCQ, hydroxychloroquine; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

Introduction

Hypoglycemia in a non-diabetic patient is always a challenge. Within the differential diagnosis is drug induced hypoglycemia. Hydroxychloroquine (HCQ) has a hypoglycemic effect that is uncommon, but well documented in the literature, both in diabetic and non-diabetic patients. We present the clinical case of a patient who presented with repeated hypoglycemia from the use of HCQ due to an Indeterminate Connective Tissue Disease. The possibility of an insulinoma was ruled out with a negative fasting test. The responsible for hypoglycemia was attributed to HCQ, where their suspension meant termination of hypoglycemia.

Clinical case

Female patient, 44 years old, with a history of thyroid follicular carcinoma treated in 2015 and Indeterminate Connective Tissue Disease. User of levothyroxine, HCQ and deflazacort. Low alcohol consumption. Since 2017 with a clinic compatible with hypoglycemia that did not have a prandial relationship, where capillary glycemia was observed between 30 and 60 mg/dL at the time of the symptomatology. At that time, she was already a HCQ user. Normal physical exam, without notable facts. Given the symptoms she had hospitalizations for hypoglycemia. In January 2018, a fasting test was performed with the following results: glycemia 50 mg/dl, insulinemia 2.3 uU/mL, cortisol 6.36 ug/dL and C-peptide 0.75 ng/ml. CT-scan of abdomen evidence normal pancreas. Normal renal and hepatic function. Cortisol was interpreted at the low limit for that glycemia by the use of deflazacort. The possibility of hypoglycemia due to HCQ is raised. Since the HCQ was very effective in controlling her rheumatologic disease, there was initial reluctance on the part of the patient for suspension. However, the patient continued to present frequent hypoglycemic symptoms with compatible capillary glycemia. Finally, in March 2018, the patient discontinued HCQ completely giving up the symptoms and a continuous glucose monitoring was performed that did not show blood glucose levels below 60 mg/dl with an average of 98 mg/dl. Subsequently, the patient continued asymptomatic.

Discussion

We present the case of a patient with a rheumatologic disease in treatment with deflazacort and HCQ who presented a compatible and demonstrated clinical presentation of hypoglycemia. Not being diabetic, the challenge is important since it is not always easy to discover the etiology of hypoglycemia in a non-diabetic patient. Anamnesis is essential where the search for drugs that can cause hypoglycemia Table 1 is a very important step to find the etiology.[1] The hypoglycemic effect of HCQ is described in the literature, but it is low frequency. Fasting tests reported in these cases show that hypoglycemia is not hyperinsulinemia.[2] In our patient, in the fasting test, although there is no complete suppression of insulin, it may be due to the fact that the hypoglycemia recorded was only 50 mg/dl, and also the lack of standardization of the methodology of the insulin measurement. On the other hand, Peptide C is low, which supports that hypoglycemia is not dependent on increased insulin secretion. In addition, insulinemia in cases of insulinomas are typically in

ranges greater than 3 or 6uU/ml in fasting tests. Hypoglycemia is an uncommon event, but it is a well-recognized adverse effect of antimalarial therapy.[3–5] Since 1925, Hughes showed that quinine could lower blood sugar, but that finding was not investigated later.[6] If not until the 1980s, cases of severe hypoglycemia begin to be published in the context of patients with severe malaria associated with the use of antimalarial drugs, particularly intravenous quinidine.[7]

Table 1 Drugs that can cause hypoglycemia

Drugs associated with hypoglycemia
Antidiabetic drugs (insulin, sulphonylureas)
Cibenzoline
Gatifloxacin
Pentamidine
Quinine/ Hydroxychloroquine
Indomethacin
Chloroquineoxaline sulfonamide
IGF-1
Lithium
Propoxyphene/ Dextropropoxyphene
Angiotensin converting enzyme inhibitors/ Angiotensin receptor antagonists
B-Adrenergic receptor antagonists

In the literature, there are few described cases of hypoglycemia with HCQ, a drug widely used for the treatment of rheumatic diseases such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE), and which are not diabetic.[2,8] On the other hand, hypoglycemia with HCQ in diabetics is also described.[5] Moreover, the use of HCQ has been shown to reduce the risk of diabetes mellitus and to improve glycemic control in patients with RA and SLE due to its hypoglycemic effect in the context of rheumatologic diseases and with the use of corticosteroids.[9–11] The exact mechanism of how antimalarials produce hypoglycemia is not clarified. In the case of quinidine and chloroquine, evidence shows that there is an increased release of insulin in studies in rats.[12] In contrast, HCQ does not appear to increase insulin secretion. The mechanisms that are postulated are: decreased insulin degradation at the cellular level, increased intracellular insulin accumulation and stimulation of insulin-mediated glucose transport.[7,13–15] Doctors and rheumatologists who prescribe HCQ should be alert to the possibility of hypoglycemia due to HCQ as well as endocrinologists and diabetologists studying hypoglycemia in the context of a non-diabetic patient. In summary, we present the clinical case of a non-diabetic patient with a rheumatic disease in treatment with HCQ who repeatedly presented hypoglycemia, that the study ruled out other causes of hypoglycemia and the suspension of HCQ determined the cessation of hypoglycemia.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

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