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Case Report

Hypoglycemic Episodes Due to Synergistic Effect of Drugs in a Woman with Diabetes and Rheumatoid Arthritis

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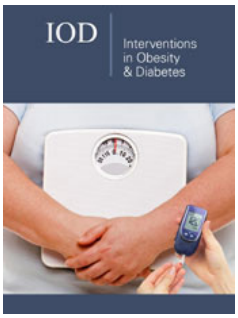

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Abstract

Hydroxychloroquine (HCQ) and Leflunomide (LE) are agents that are commonly used to treat rheumatoid arthritis. Type 2 Diabetes (DM2) patients are in increased risk of hypoglycemia. The present report documents a case of repeated dawn hypoglycemic episodes due to concomitant use of HCQ, LE and Repaglinide in a patient with Rheumatoid arthritis and DM2.

Keywords: Hydroxychloroquine, Leflunomide, Repaglinide, Hypoglycemia, Type 2 Diabetes, Rheumatoid arthritis

Abbreviations: HCQ: Hydroxy Chloro Quine; LEF: Leflunomide; DM2: Type 2 Diabetes; RA: Rheumatoid Arthritis; RE: Repaglinide; HYPO: Hypoglycemia; SITA: Sitagliptin

Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug with anti-inflammatory properties that is employed in rheumatic diseases. Remarkable glucose lowering side effect of HCQ in non diabetic and diabetic patients is reported in literature [1-3]. Drug interactions can sometimes provoke to patients synergistic unexpected disturbing side effects; this is our case.

Case Presentation

A 49 year-old woman was first seen in our internal medicine outpatient clinic 3 months ago. Her past medical history included diabetes mellitus type 2 (DM2) for 5 years, seronegative rheumatoid arthritis (RA) for 4 years and hypertension. Her long-standing medications at that time included leflunomide (LE) 10mg daily, HCQ 200mg twice a day, prednisone 10mg daily, irbesartan 150mg daily, sitagliptin (SITA) 100mg daily, metformin 1000mg twice a day. Four months before our meeting her hemoglobin A1c was 5, 8%, while it raised to 8% at her last control 10 days before she came to us. After the last result she referred to her general practitioner and he added SITA 100mg to her previous antidiabetic treatment that included only metformin 1000mg twice a day (morning and dinner time). After a week she referred to out clinic worried due to some recent high blood glucose (BG) levels during the morning and persistent high during the day. She referred no symptoms of hypoglycemia (HYPO) at that time. After controlling her glucometer data I confirmed the high BG levels during the day. Repaglinide (RE) 1mg twice a day before lunch and dinner was administered to her, while she continued also her previous medications. A schedule with three times per day BG measurement for a week was given to the patient prior to discharge. Our next appointment was programmed after a week.

The patient returned to our clinic reporting episodes of HYPO every morning. She reported glucometer readings approximating 50-65mg/dl during these events. Instead, her glucometer reading were high normal during the day. Her HYPO symptoms included diaphoresis, hunger, anxiety and tremulousness. She reported no alcohol intake neither modification of diet habits during the last weeks. After my advice she discontinued her evening RE 1mg dose, while I transferred her second metformin dose uptake noontime instead of dinnertime.

She continued her other long-standing medications. A schedule with three times per day BG measurement for a week was given to the patient prior to discharge. Our next appointment was programmed after a week. She returned on her appointment to our clinic reporting still, but milder HYPO episodes. Her glucometer readings were approximating 60-75mg/dl during these events. Her glucometer reading were high normal during the day. SITA's dosage was decreased to 50mg daily after breakfast, while her noontime metformin uptake was decreased to 850mg. She continued her other long-standing medications. A schedule with frequent BG measurement was given to the patient while our next appointment was programmed after 15 days. At our visit, she reported random fasting finger sticks in the 110-120mg/dl range, and random sticks 2 hours after meal in the 140-180mg/dl range. She reported no HYPO episodes. She was discharged with the same long-standing medications, while a schedule with daily BG measurement was given to her and the next appointment was arranged after 3 months.

Discussion

Diabetic patients are prone to HYPO episodes. In our case, to a patient that was taking sitagliptin and metformin (drugs that rarely cause HYPO when administered as the only therapy), RE was also added in order to control hyperglycemia. Her long-standing medications also included LEF and HCQ. Glucose lowering side effect of HCQ in diabetic patients is reported in literature [1,3] Although the HCQ mechanism has not been clarified yet, increased insulin sensitivity and beta cell function [4-8] as well as decreased insulin degradation [3,6,8], is suggested to contribute to the reduction in serum glucose levels. Furthermore, after the HYPO episodes I proceeded to an extensive control of Summary of Product Characteristics (SPC) of all medications the patient was taking. This patient was taking the anti-rheumatic drug LE, while RE was added in order to optimize glycemic control of her diabetes. As is reported to LE's SPC, its concomitant administration with RE, increases RE's Cmax (maximum concentration of the drug) and AUC (Area under the curve that indicates the drug's concentration in blood plasma) by 1,7 and 2,4 times respectively. This, according LE's SPC, occurs because LE is an ''*in vivo*'' Cytochrome P4502C8 inhibitor, meanwhile RE is degradated through this enzyme. To this patient the concomitant administration of HCQ, LE and RE to a DM2 patient led to recurrent HYPO episodes during the night and morning, even if the patient had high BG levels days before RE administration. The HYPO episodes persisted even when RE and Metformin dinnertime dose were discontinued. The HYPO's vanished only when patient's previous antidiabetic treatment was drastically reduced and all dinnertime antidiabetic drugs were discontinued.

Diabetic patients are prone to HYPOS. Clinicians prescribing to them multiple drugs for other diseases should be aware that drug interactions can provoke to these patients synergistic unexpected disturbing side effects. Moreover, these patients should monitor closely their BG levels in order to prevent unexpected HYPO episodes.

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