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Reminder of important clinical lesson

Hydroxychloroquine: a diabetic drug in disguise?

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Abstract

Hydroxychloroquine (HCQ) is an antimalarial agent that is commonly used to treat rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The present report documents a case of hypoglycaemia due to HCQ in a patient with SLE and diabetes mellitus type 2, in which the HCQ completely replaced the need for daily subcutaneous insulin.

BACKGROUND

A substantial proportion[1] of patients with rheumatoid arthritis (RA) carry a diagnosis of diabetes, and many of these patients will fall under the care of non-rheumatologists for their comorbidities. Hydroxychloroquine (HCQ) has been known to have a potent hypoglycaemic effect, and in the past had been studied only in small, relatively unknown trials as a treatment of diabetes mellitus type 2. Recently, this interest has decreased, despite some recent data that may indicate a protective role of HCQ against the onset of diabetes.[2] Our case study is a reminder of the potency of the hypoglycaemic effect that HCQ carries, and a call to reinvestigate its role in the treatment of diabetes itself.

CASE PRESENTATION

A 49 year-old woman was seen in our internal medicine clinic. Her past medical history included diabetes mellitus type 2 for 2 years, hypertension, systemic lupus erythematosus (SLE) diagnosed in 1986 and sensorineural hearing loss. At 2 months prior to presentation, she had her first visit with a new rheumatologist and was prescribed HCQ 200 mg twice daily. Other long-

standing medications at that time included methotrexate 10 mg weekly, prednisone 10 mg daily, rosiglitazone 8 mg daily, insulin glargine 25 units daily, aspirin 81 mg daily, hydrochlorothiazide 25 mg/triamterene 37.5 mg daily and folic acid 1 mg daily. Her most recent haemoglobin A1c was 6.2%. She had previously been prescribed HCQ approximately 1 year prior but had quickly discontinued it due to stomach upset. She had not noticed any symptoms of hypoglycaemia at that time.

At our outpatient internal medicine evaluation, the patient reported episodes of hypoglycaemia immediately after the initiation of HCQ. Her symptoms included diaphoresis, hunger, nausea and tremulousness. She reported glucometer readings approximating 50 mg/dl during these events. She discontinued the 25 units of insulin glargine, but continued the HCQ, rosiglitazone and her other medications. Her finger sticks normalised within 2 days. At our visit, she reported random finger sticks in the 110–120 mg/dl range. At 2 months after discontinuing her insulin and beginning the HCQ, a repeat haemoglobin A1C had decreased to 5.7%.

OUTCOME AND FOLLOW-UP

At 6 months later her rosiglitazone 8 mg was changed to pioglitazone 45 mg per day, after she expressed concerns about risks regarding rosiglitazone. Her subsequent haemoglobin A1C after this change was 5.8%. Her most recent ophthalmologic exam showed no signs of HCQ toxicity or diabetic retinopathy, and she has not reported any other side effects from this treatment.

DISCUSSION

Antimalarials such as HCQ and chloroquine (CQ) have been long known to cause hypoglycaemia. The mode of hypoglycaemic action may occur due to inhibition of intracellular degradation of insulin,[3] increased insulin secretion in pancreatic islet cells,[4] and inhibition of hepatocyte gluconeogenesis.[5] HCQ appears to have a linear dose-effect relationship for increasing insulin levels over a range of HCQ concentrations.[6] Though HCQ has become the medication of choice in rheumatic diseases due to its decreased ocular toxicity compared to CQ,[7] we reviewed the following case reports and trials of both medications in order to better understand any potential “class effect” seen for their usage in patients with diabetes.

We searched PubMed and found three case reports that looked at HCQ or CQ usage in the setting of patients with diabetes. Two reports focused on extremely resistant diabetes mellitus type 1 in the inpatient setting that required remarkably large amounts of intravenous insulin.[8,9] In both cases the insulin requirements dramatically decreased after the usage of the antimalarial. A third case study documented severe hypoglycaemia requiring two emergency room visits in a patient with diabetes mellitus type 2 on a standard outpatient diabetic medication regimen while taking HCQ. This patient eventually required a decreased dose of insulin,[10] whereas our patient no longer required any insulin therapy at all.

We also briefly reviewed study trials to look at HCQ and CQ in the treatment of patients with diabetes. Of the five trials we found, four were outdated, too small, with clinically irrelevant or

only short-term outcomes.[11–14] One study, with a reasonable clinical endpoint of long-term Hgb A1c improvement, had only 38 patients and poorly defined randomisation.[15]

This review highlights the need to re-examine HCQ as a specific treatment modality for diabetes mellitus type 2, in patients with and without coexisting rheumatic diseases. HCQ has an established track record in the treatment of rheumatic conditions and appears to be well tolerated and relatively inexpensive. Given the cardiovascular morbidity associated with diabetes, RA and SLE, the reported antiplatelet and lipid lowering effects[16,17] of these agents may provide additional rationale for their use.

This case report illustrates the need for internists, rheumatologists and endocrinologists to have a heightened awareness of the potential magnitude of the hypoglycaemic effect that HCQ and CQ can have. Patients with diabetes need education on the possibility of life-threatening hypoglycaemia after starting treatment with HCQ or CQ. Within the days after instituting antimalarial treatment, there needs to be open communication between patient and provider in order to anticipate and identify this occurrence and make appropriate adjustments in diabetic medications.

LEARNING POINTS

- Patients with diabetes on hypoglycaemia-inducing medications need to closely monitor their blood sugar when starting hydroxychloroquine (HCQ).
- Physicians caring for patients with diabetes with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) need to be educated about this side effect and appropriately titrate diabetes medications.
- More studies investigating HCQ as a diabetic medication are needed.

Footnotes

Competing interests: None.

Patient consent: Patient/guardian consent was obtained for publication.

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