CASE REPORT

Hydroxychloroquine-induced hypoglycaemia in non-diabetic renal patient on peritoneal dialysis

Ahmed El-Solia,[1] Khalid Al-Otaibi,[2] Abdullah K Al-Hwiesh[3]

[1]Renal Department, Southend University Hospital NHS Foundation Trust, Westcliff-on-Sea, Essex, UK
[2]Urology Department, Abdulrahman Bin Faisal University, King Fahd Hospital of the University, Dammam, Saudi Arabia
[3]Internal Medicine Department, Nephrology Division, Imam Abdulrahman Bin Faisal University, King Fahd Hospital of the University, Dammam, Saudi Arabia

Correspondence to
Dr Ahmed El-Solia,
dr_ahmed_solia@yahoo.com

Accepted 7 April 2018

To cite: El-Solia A, Al-Otaibi K, Al-Hwiesh AK. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-223639

SUMMARY

Hydroxychloroquine (HCQ) is a commonly used drug for the treatment of systemic lupus erythematosus (SLE). Renal involvement is common in SLE. We present a 25-year-old woman with lupus nephritis on peritoneal dialysis whose lupus was quite silent for almost three years, and secondary to HCQ she developed severe hypoglycaemic episodes, which were completely resolved after stopping HCQ.

BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystem disease; clinical presentations may vary from mild skin reaction to life-threatening major organ dysfunction. Lupus can cause serious renal damage up to complete loss of kidney function. HCQ is a background therapy in lupus management.[1] HCQ can affect glucose homeostasis and may lead to serious hypoglycaemia episodes in both diabetic and non-diabetic population. The optimal HCQ dosing in patients on dialysis is still open to debate. We present a case of SLE on peritoneal dialysis who had a severe hypoglycaemic episodes related to HCQ and we will review the literature about the glycaemic effects of HCQ as well as its renal dose.

CASE PRESENTATION

A 25-year-old woman with chronic kidney disease stage 5D secondary to lupus nephritis presented to the emergency department with disturbed conscious level. Her blood sugar was 0.5 mmol/L; therefore, she was administered 50 mL intravenous dextrose 50%, and consequently, her blood sugar has picked up and she regained her consciousness.

Her medical history includes hypertension, vitiligo and SLE since childhood. She had lupus nephritis that progressed into end-stage renal disease requiring dialysis 3 years ago. Since that time, her lupus was not clinically active despite persistent abnormal serological markers in the form of low C3 and high dsDNA titres.

Her medications were HCQ 200 mg daily (started around 4 years ago), cellcept 500 mg twice per day, prednisolone 10 mg/day, atenolol 50 mg daily, furosemide, amlodipine, pantoprazole, alfacalcidol and calcium carbonate. There was no history of other drug use or hypoglycaemic agents.

She had headache, anorexia and mild abdominal discomfort when she regained her consciousness, but she was apparently well prior to this episode. No clinical pictures suggested peritonitis or neurological deficit. She was admitted to investigate the causes of her hypoglycaemia. During hospitalisation, she developed recurrent hypoglycaemic episodes reaching 1.67 mmol/L, consequently, she was maintained on intravenous dextrose 25% and stress dose steroid (hydrocortisone 100 mg intravenous every 8 hours).

She was stable on automated peritoneal dialysis (APD) with no recent changes in her prescription. Her usual APD prescription was dianeal 1.36% 5 L and 2.27% 5 L over 9 hour each fill 1.9 L and last fill of icodextrin 1.5 L. Her creatinine clearance and dialysis adequay (Kt/V) were maintained over almost 9 months around 1.6 and 2 mL/min, respectively.

INVESTIGATIONS

We carried out investigations in the form of renal, liver, haematological, thyroid function tests, infection parameters, virology (hepatitis C, hepatitis B and HIV) and peritoneal fluid examination. All revealed non-significant abnormalities apart from high lipase level up to threefold the upper normal range with normal amylase. During a hypoglycaemia episode, further blood tests to exclude insulinoma revealed insulin 27 µU/mL (reference range 6–27 µU/mL) and C-peptide level 18.8 ng/mL (reference range 1.1–4.4 ng/mL). Morning cortisol level was 13.7 µg/dL (reference range 3.7–19.4 µg/dL).

For the sake of preserving the residual renal function, non-contrast MRI of the abdomen was the modality of choice and the images did not suggest insulinoma as a potential cause.

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses for recurrent spontaneous hypoglycaemia are as follows.

- Insulinoma, less likely as insulin level was not high enough to consider it in diagnosis; moreover, imaging of the abdomen did not suggest any pathology.
- Addisonian disease, it was excluded on clinical and laboratory basis.
- Exogenous drugs as insulin and sulfonylurea were excluded by history; in addition, there was no history of alcohol or illicit drug intake.
- Pancreatitis, first, there was no clinical picture that suggested this diagnosis. Second, MRI did not show evidence of SLE-induced pancreatitis. Lastly, pancreatitis in SLE would present with hyperglycaemia instead of hypoglycaemia. Serum lipase roughly up to threefold increase, which was a non-significant figure in patients

Table 1 Case reports of the hypoglyceamic effects of HCQ

Case report	Cansu *et al*[15]	Winter *et al*[16]	Kumru *et al*[17]	Kang *et al*[18]	Ünübol *et al*[19]	Current study
Gender	Male	Female	Female	Female	Female	Female
Age	62	80	66	49	49	25
Comorbidities	RA	HTN, ACS, MGUS, mild inflammatory OA	RA, pyoderma gangrenosum	SLE, HTN, SNHL, DM	RA	CKD 5D, SLE, HTN, vitiligo
DM	No	No	No	Yes	First discovered after DC of HCQ	No
Renal status	NA	Mild	No	NA	No	CKD 5 on APD
HCQ dose/day	200 mg	400 mg	NA	400 mg	200 mg	200 mg
Duration between HCQ and hypoglycaemia	4 months	4 months	Soon after first dose	Soon after start	4 years	4 years
Blood sugar during the attack	10 mg/dL	Unpredictable and after bolus it reached 24.	28 mg/dL	50 on antidiabetic drugs which was stopped	15 mg/dL	9 mg/dL
Recurrence of hypoglycaemia	Recurrent attacks for 10 days after DC	Recurrent episodes during treatment with HCQ	Recurrent for 10 hours after DC HCQ	NA	Recurrent	Recurrent for 16 hours after DC HCQ

ACS, acute coronary syndrome; CKD 5D, chronic kidney disease stage 5D; DC, discontinue; DM, diabetes mellitus; HCQ, hydroxychloroquine; HTN, hypertension; MGUS, monoclonal gammopathy of undetermined significance; NA, data not available.; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNHL, sensory neural hearing loss.

with uraemia.[2] Serum amylase was normal as icodextrin competitively interacts as a substrate in its assay.[3]

OUTCOME AND FOLLOW-UP

HCQ was stopped for its potential hypoglycaemic effect reported in the literature. She has not developed any hypoglycaemic attacks over 5 months follow-up since discharge. In addition, her fasting blood sugar and haemoglobin A1C are well controlled.

DISCUSSION

HCQ and its hypoglycaemic effect have been reported in number of cases (table 1). To the best of our knowledge, this is the first case report in literature of HCQ-induced hypoglycaemia in end-stage renal failure on peritoneal dialysis.

She was maintained on HCQ for 4 years without any hypoglycaemic attacks and she started developing these recurrent episodes with no warning or obvious cause like medications or dialysis prescription changes. In addition, her creatinine clearance and residual kidney function were stable over a long period, which suggested no changes in drug excretion.

HCQ can affect insulin haemostasis by different mechanisms. First, it decreases insulin clearance rather than stimulating its secretion as suggested by in vitro and human studies.[4 5] Second, HCQ lowers insulin resistance[6]; thus, it has been studied as a possible antidiabetic drug and it has shown to improve the glycaemic control in patient with diabetes.[7] Moreover, it is associated with a lower fasting glucose in a population of non-diabetic women with rheumatological disease.[6]

HCQ also has a primary preventive role against new-onset diabetes in rheumatoid arthritis as suggested by large prospective multicentre study over 21 year; the incident of newly diagnosed diabetes mellitus (DM) was significantly lower in the HCQ group compared with non-HCQ group, 5.2–8.9 per 1000 patient-years, respectively.[8]

Similarly for patients with lupus, Chen *et al* reported the adjusted HR for DM in HCQ exposed group was 0.26 (95% CI 0.18 to 0.37) if compared with those never used HCQ, adjusted for daily glucocorticoid dose. This effect was believed to be in a dose-dependent manner.[9]

HCQ dosing in renal failure is variable and no dose adjustment according to the renal state is provided in majority of SLE cases.[10] HCQ overdosing and under treatment is associated with undesirable outcome. Durcan *et al*, have concluded that a lower HCQ level in the blood in patients with renal dysfunction is associated with a higher lupus activity.[11] In addition, renal impairment is a risk factor for development of HCQ-induced cardiotoxicity, peripheral neuropathy and proximal myopathy.[12 13] Therefore, the prescribing healthcare professionals should be cautious for patient with mild renal impairment and monitor plasma level in case of severe renal failure.[14]

Learning points

- Hydroxychloroquine (HCQ)-induced hypoglycaemia can occur in patients on peritoneal dialysis despite the glucose content in the peritoneal dialysis fluid.
- Frequent monitoring of blood sugar is advisable during treatment.
- Blood HCQ level should be considered in patients with renal impairment.

Contributors AE-S has reviewed the literature and written the first draft. KA-O and AKA-H have participated in the discussion section and revised the draft for the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, *et al*. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;69:20-8.
2 Royse VL, Jensen DM, Corwin HL. Pancreatic enzymes in chronic renal failure. *Arch Intern Med* 1987;147:537–9.
3 Jiang CF, Kw N, Tan SW, *et al*. Serum level of amylase and lipase in various stages of chronic renal insufficiency. *Zhonghua yi xue za zhi= Chinese medical journal; Free China ed* 2002;65:49–54.
4 Emami J, Pasutto FM, Mercer JR, *et al*. Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. *Life Sci* 1998;64:325–35.

5 Blazar BR, Whitley CB, Kitabchi AE, *et al*. In vivo chloroquine-induced inhibition of insulin degradation in a diabetic patient with severe insulin resistance. *Diabetes* 1984;33:1133–7.
6. Penn SK, Kao AH, Schott LL, *et al*. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 2010;37:1136–42.
7. Gerstein HC, Thorpe KE, Taylor DW, *et al*. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas– a randomized trial. *Diabetes Res Clin Pract* 2002;55:209–19.
8 Wasko MCM, Hubert HB, Lingala VB, *et al*. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007;298:187–93.
9 Chen Y-M, Lin C-H, Lan T-H, *et al*. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology* 2015;54:1244–9.
10 Bethel M, Yang FM, Li S, *et al*. Hydroxychloroquine in patients with systemic lupus erythematosus with end-stage renal disease. *J Investig Med* 2016;64:908–10.
11 Durcan LJ, Clarke WA, Magder L, *et al*. OP0187 Hydroxychloroquine blood levels in SLE: clarifying dosing controversies and improving adherence. *Ann Rheum Dis* 2015;74:142.2–3.
12 Nord JE, Shah PK, Rinaldi RZ, *et al*. *Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. In: Seminars in arthritis and rheumatism*. , 2004:33, 336–51. WB Saunders.
13 Stein M, Bell MJ, Ang LC. Hydroxychloroquine neuromyotoxicity. *J Rheumatol* 2000;27:2927–31.
14 National Institute for Health and Care Excellence. Hydroxychloroquine sulfate | Drug | BNF provided by NICE [Internet]. Bnf.nice.org.uk 2017 https://bnf.nice.org.uk/drug/hydroxychloroquine-sulfate.html (cited 21 Oct 2017).
15 DÜ C, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. *Rheumatology* 2008.
16 Winter EM, Schrander-van der Meer A, Eustatia-Rutten C, *et al*. Hydroxychloroquine as a glucose lowering drug. *BMJ Case Rep* 2011;2011:bcr0620114393.
17. Kumru AM, Rouse M, Vansaghi LM, *et al*. Hydroxychloroquine associated hyperinsulinemic hypoglycemia. *Kansas Journal of Medicine* 2013.
18 Kang L, Mikuls TR, O'Dell JR. Hydroxychloroquine: a diabetic drug in disguise? *BMJ Case Rep* 2009;2009:bcr0820080654.
19 Ünübol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. *J Clin Rheumatol* 2011;17:46–7.