Unexpected outcome (positive or negative) including adverse drug reactions

Hydroxychloroquine as a glucose lowering drug

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Correspondence to Dr Elizabeth Martha Winter, lieswinter@xs4all.nl**Summary**

The authors report a remarkable glucose lowering side effect of the often used drug hydroxychloroquine (Plaquenil) in an otherwise healthy non-diabetic patient, who presented with severe hypoglycaemia. Although the mechanism has not been clarified yet, increased insulin sensitivity as well as decreased insulin degradation is suggested to contribute to the reduction in serum glucose levels. Clinicians prescribing this drug must be warranted and check glucose levels in the initial phase. Moreover, hydroxychloroquine might be applied as therapeutic in refractory diabetic rheumatics or rheumatic patients at risk to develop diabetes mellitus.

BACKGROUND

Antimalarials are commonly prescribed drugs in the treatment of rheumatic disease. We hereby present a case in which recurrent severe hypoglycaemias in a non-diabetic healthy individual appeared to be provoked by the application of hydroxychloroquine (HCQ) or Plaquenil. This unexpected hypoglycaemic effect of HCQ has only once been described before in a non-diabetic,¹ and occasionally in diabetics.²⁻³ The induction of glucose tolerance by its non-synthetic counterpart quinine is better known but rare.² The knowledge of this side effect of HCQ is important for clinicians prescribing this drug. They must regularly check glucose levels in the initial phase. Moreover, they might consider application of HCQ in refractory diabetic rheumatics as well as in rheumatic patients at risk for developing diabetes mellitus (DM), since HCQ has been demonstrated to diminish the risk of acquiring DM as well as to lower the cardiovascular risk.⁴⁻⁵

CASE PRESENTATION

An 80-year-old woman was admitted to our hospital after being found in a comatose condition. Heteroanamnesis told us that she had been little confused and frightened the evening before. In the ambulance, glucose level was too low to be measured. After intravenous administration of 15 ml of glucose 50%, glucose level was found to be 1.3 mmol/l. Only with another dose of 25 ml, the patient regained consciousness and glucose value normalised.

In the past months, she had demonstrated three other events of abrupt syncope and loss of consciousness due to proven hypoglycaemia. She had lost weight in the last year (she could not specify the amount). Her history consisted of mild renal insufficiency, M-protein of unknown significance, hypertension, osteoarthritis with mild inflammatory characteristics and one event of acute coronary syndrome. She was using HCQ, carbasalatcalcium, nifedipine, metoprolol, paracetamol and zolpidem.

On physical examination, no abnormalities were observed; temperature, pulse rate, blood pressure and saturation were all within normal ranges. Her appearance was in accordance with biological age. Investigation of heart, pulmones, abdomen and extremities did not reveal any

irregularities, neither did neurological examination. Standard blood analysis demonstrated no changes compared to previous laboratory investigation with a normocytic anaemia, slightly elevated infection parameters and minor disturbed renal function. Electrolytes, leucocyte count, thrombocyte count and liver function tests were normal.

INVESTIGATIONS

The patient was hospitalised to investigate the cause of her hypoglycaemia. Survey for hyperinsulinemic conditions was done by determination of serum insulin and C-peptide levels during 72 h of fasting test. The test was stopped at the 62nd h because of hypoglycaemia with glucose 2.5 mmol/l. Insulin and C-peptide levels were found to be within normal ranges at the end of the test (<2 mU/l and 0.28 nmol/l, respectively). Laboratory investigation for thyroid or adrenal dysfunction (including adrenocorticotrophic hormone stimulation test) did not reveal any abnormalities. No findings suggestive of malignancy were observed in either abdominal echography, chest x-ray, abdominal CT scan, or cerebral CT scan. As reported, her drugs did not include any oral antidiabetics or insulin, she did not use any alcohol.

DIFFERENTIAL DIAGNOSIS

For a healthy-appearing non-diabetic individual demonstrating spontaneous hypoglycaemia, the differential diagnosis consists of laboratory sampling error, hormone deficiencies, endogenous hyperinsulinism and usage of insulin, sulfonylurea and certain other drugs.

OUTCOME AND FOLLOW-UP

With one case report in 2008 describing induction of hypoglycaemia by HCQ in a non-DM patient¹ we questioned whether her HCQ usage (400 mg daily) could have caused the hypoglycaemic events. She appeared to take the medication since 4 months, with all four reported hypoglycaemic incidents within this time window. The medicament was stopped, and the hypoglycaemias did not recur. Follow-up consists of 24 months now, with no further incidents reported.

DISCUSSION

We report a case of severe hypoglycaemias due to HCQ usage, with four reported events of symptomatic hypoglycaemias within the clear-cut time window of 4 months of HCQ application. After discontinuation, no new incidents were reported. This side effect of HCQ in non-DM patients has been reported once,¹ with another case describing a patient who appeared to have masked DM due to HCQ usage⁶ and a case within a known DM patient.⁷

The other causes of hypoglycaemia mentioned previously were considered unlikely. Since our patient had numerous hypoglycaemias reported, without other overt biochemical abnormalities like leucocytosis, a biochemical sampling error did not exist. As discussed above, thyroid and adrenal functioning were normal. Insulinoma was excluded by low insulin levels during fasting test. Besides, our patient reported weight loss instead of weight gain, with the latter being typical for insulinoma. Radiographic investigation did not reveal any tumour process, making insulin like growth factor (IGF)-producing tumour and nesidioblastosis unlikely. Moreover, the patient lacked postprandial hypoglycaemia, compatible with nesidioblastosis. Although IGF-producing tumours are usually large and easily visualised during radiographic analysis, while patients appear ill, the former should have been excluded through biochemical testing. We highly recommend this to be done in future similar cases within an early stage of investigation. Another disorder which was not excluded in our case was the presence of antibodies against insulin, which might cause haphazard dissemination and release of free insulin into the circulation.⁸ However detected, presence of antibodies appears to be unspecific and therefore not generally recommended.⁸ Although our patient reported no usages of insulin or sulfonylurea, this should also have been tested during fasting test. Nevertheless, regarding the fact that withdrawal of HCQ resulted in absolute disappearance of the hypoglycaemic events during 2 years, with sole presentation of them during the 4-months of HCQ application, we consider HCQ as the definite cause for the glucose lowering.

The underlying mechanism for this side effect of HCQ has not been clarified until now. A decreased degradation rather than increased secretion of insulin is suggested by both in vitro experiments^{9 10} as well as a randomised clinical trial. For the latter, Quatraro *et al* demonstrated decreased insulin requirements in DMII patients without altered C-peptide levels, thereby suggesting unaltered secretion of insulin.¹¹ Decreased insulin resistance has also been suggested to contribute, as demonstrated for patients with systemic lupus erythematosus.⁵ A large prospective cohort study among rheumatoid arthritis patients showed that use of HCQ was associated with decreased risk of DMII development.⁴

Moreover, cardiovascular risk is diminished by HCQ usage⁵ with a more beneficial lipid profile and decreased diastolic blood pressure.¹² Although long-term use of chloroquine is associated with congestive heart failure and rhythm disturbances, HCQ can be considered safe,^{13 14} even if risk factors like renal failure, high-dose therapy, and pre-existing cardiac disease are present.¹⁴ If on digoxin therapy, caution is needed because of the interaction between these drugs.

Due to limited literature, a specific profile for a patient at risk to develop hypoglycaemia as a result of HCQ use can not be described. We therefore advise regular glucose

controls for all patients during the initial phase. However, since the hypoglycaemic effect of HCQ is described to be dose-dependent,¹⁵ while the often coprescribed drug prednisone is known for its hyperglycemic effect, we suggest extra caution for patients on high-dose HCQ not taking prednisone as comedication.

In conclusion, HCQ can lower glucose levels. Clinicians must be warranted for hypoglycaemia during HCQ usage. Treatment with HCQ might be considered as therapeutic in refractory diabetic rheumatics¹¹ and in rheumatic patients at risk to develop DMII,⁴ especially since HCQ is suggested to lower cardiovascular risk of this patient group,⁵ without adverse cardiovascular effects.^{13 14}

Learning points

- ▶ HCQ might lower glucose levels even in non-DM patients possibly leading to severe hypoglycaemias.
- ▶ During HCQ prescription, glucose levels must be verified in the initial phase.
- ▶ HCQ application might be considered in refractory diabetic rheumatics since it brings down glucose levels.
- ▶ HCQ might be applied in rheumatic patients at risk to develop DM, especially since HCQ is demonstrated to reduce cardiovascular risk.

Competing interests None.

Patient consent Obtained.

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