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Insulin sparing effect of hydroxychloroquine in uncontrolled diabetes mellitus

ABSTRACT

Hydroxychloroquine (HCQ) has a favorable glycemic effect that provides a rationale for its use in diabetes mellitus. Decreased insulin degradation and increased insulin sensitivity is suggested to contribute to the reduction in serum glucose levels. Herein, we present a case on the beneficial impact of HCQ on glycemic control in diabetes mellitus.

A 69-year old female suffering from type 2 diabetes mellitus presented to the clinic for routine follow up. For management of diabetes she was taking glimepiride 4mg once daily, combination of metformin and sitagliptin (1000/50 mg) twice daily and 94 units of insulin/day. Baseline fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels were 183 and 222 mg/dL respectively and glycosylated hemoglobin A (HbA_{1c}) level was 8.4%. To achieve glycemic control HCQ 400 mg once daily was initiated as an add on antidiabetic drug.

HbA_{1c} level decreased to 6.9% at four months and to 6.8% at eight months after HCQ was utilized. FPG level decreased to 110 mg/dL at six months and to 114 mg/dL at eight months. PPG level decreased to 178 mg/dL at six months and 130 mg/dL at eight months. Thus the FPG level decreased by 69 mg/dL and PPG level decreased by 92 mg/dL respectively from baseline. Acknowledging the progressive positive response to antidiabetic agents, the insulin dose was decreased to

56 units/day at four months, 42 units/day at six months and 28 units/day at eight months.

The case highlights the potential ability of HCQ to lower HbA_{1c} and decrease insulin requirement in uncontrolled diabetic patients. (Clin Diabetol 2016; 5, 4: 138-140)

Key words: hydroxychloroquine, diabetes mellitus, insulin, hyperglycemia, HbA_{1c}

Introduction

Approximately 50% of Indian respondents had poor diabetes control in a multi-country study conducted in Asia [1]. Uncontrolled hyperglycemia has deleterious effects on the human vascular tree and are the major source of morbidity and mortality in type 2 diabetes mellitus (T2DM). One or more oral antidiabetic treatment options are required by most patients such as metformin along with sulfonylurea, thiazolidinedione and DPP-4 inhibitor. Many patients eventually require insulin therapy. In patients with suboptimal blood glucose control, especially those requiring increasing insulin doses, adjunctive use of novel antidiabetics agents may be helpful in improving glucose control and reducing the amount of insulin needed.

Hydroxychloroquine: novel antidiabetic drug

Hydroxychloroquine (HCQ) has a unique mode of action which is different from other antidiabetic drugs. It causes inhibition of insulin degradation in cells thus enhancing the metabolic effects of the hormone and has also shown to improve insulin sensitivity in non-diabetic obese individuals [2].

An epidemiological study has reported 77% reduction in development of diabetes in rheumatoid arthritis patients with HCQ use for more than four years com-

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pared to never users. It is known to reduce cardiovascular risk in rheumatoid arthritis and lupus patients [3]. The release of various inflammatory mediators are believed to play a critical role in insulin resistance, β -cell dysfunction, dyslipidemia as well as atherosclerosis. The anti-inflammatory effects exerted by HCQ are noteworthy since these pathogenic mechanisms are implicated in the progression to T2DM [2]. It is approved in India as an adjunct to improve glycemic control of patients on metformin and sulfonylurea combination in T2DM.

Glycemic control with HCQ

Hydroxychloroquine has shown a positive effect on glycemic control in patients with diabetes and may provide a means for better disease management. Quatraro A et al. [4] noted that there was more decrease in glycemic profile (-11.7 mmol/L vs -0.9 mmol/L) and HbA_{1c} level (-3.3% vs -0.3%) in patients treated with insulin and HCQ 400 mg as compared to patients treated with insulin and placebo. The daily insulin dose of patients in the HCQ group also had to be reduced by an average of 30% [4]. Pareek et al. [2] showed that HCQ 400 mg has comparable hypoglycemic effects to those of pioglitazone 15 mg as a third-line treatment in T2DM patients inadequately controlled on a combination of glimepiride or gliclazide and metformin. Hence consideration may be given for addition of HCQ in uncontrolled diabetics.

Case presentation

A 69-year old female suffering from type 2 diabetes mellitus since nine years and one month presented for routine health check up. Her past medical history includes hypertension with ischemic heart disease. On examination blood pressure (BP) was 100/70 mm Hg, weight was 90.7 kg and body mass index (BMI) was 33.7 kg/m². No abnormal findings were detected on systemic examination. For management of blood glucose levels she was taking glimepiride 4mg once daily, combination of metformin and sitagliptin (1000/50 mg) twice daily and biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin 44 units in morning and 50 units in evening. She was also taking aspirin 150 mg, ator-

vastatin 10 mg, telmisartan 40 mg and multivitamin multimineral supplements.

Laboratory investigations revealed that the fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels were 183 and 222 mg/dL respectively and HbA_{1c} level was 8.4%. As the plasma glucose levels were uncontrolled and target HbA_{1c} was not achieved she was prescribed HCQ 400 mg once daily as an add on drug to the current antidiabetics and was asked to follow-up after 3 months. Baseline ophthalmological examination was conducted before initiation of HCQ and was normal.

Outcome and follow-up

Subsequent follow-up visit at four months revealed that the HbA_{1c} level had decreased to 6.9% and random plasma glucose (RPG) level was 167.3 mg/dL. Blood pressure was 140/90 mm Hg at this visit. As the target HbA_{1c} was achieved and plasma glucose level was under control the insulin dose was decreased to 26 units in morning and 30 units in evening. Other medications were continued unchanged.

FPG and PPG levels at six months follow-up visit decreased to 110 and 178 mg/dL respectively. Blood pressure was 140/70 mm Hg at this visit. Acknowledging the positive response to antidiabetic agents, the insulin dose was further decreased to 22 units in morning and 20 units in evening. There was a further decrease in HbA_{1c} level at eight months to 6.8% accompanied by a decrease in FPG and PPG to 114 mg/dL and 130 mg/dL respectively (Table 1). RPG has also decreased to 86.6 mg/dL. At this visit BP was 143/72 mm Hg, weight was 89.4 kg and BMI was 33.2 kg/m². The insulin dose was decreased to 12 units in the morning and 16 units in the evening. All the therapies were well tolerated and she did not report any fresh complaints at this visit.

Discussion

Lifestyle and environmental changes over the last century have resulted in a dramatic increase in the incidence of diabetes in India. Prevention of diabetes and control of its micro- and macrovascular complications will require an integrated approach to cause significant reduction in the huge premature morbidity and mortality.

Table 1. Fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels at baseline, 6 and 8 months of HCQ therapy

| Plasma glucose levels | Baseline | 6 months | 8 months | Decrease from baseline |
|-----------------------|----------|----------|----------|------------------------|
| FPG [mg/dL] | 183 | 110 | 114 | -69 |
| PPG [mg/dL] | 222 | 178 | 130 | -92 |

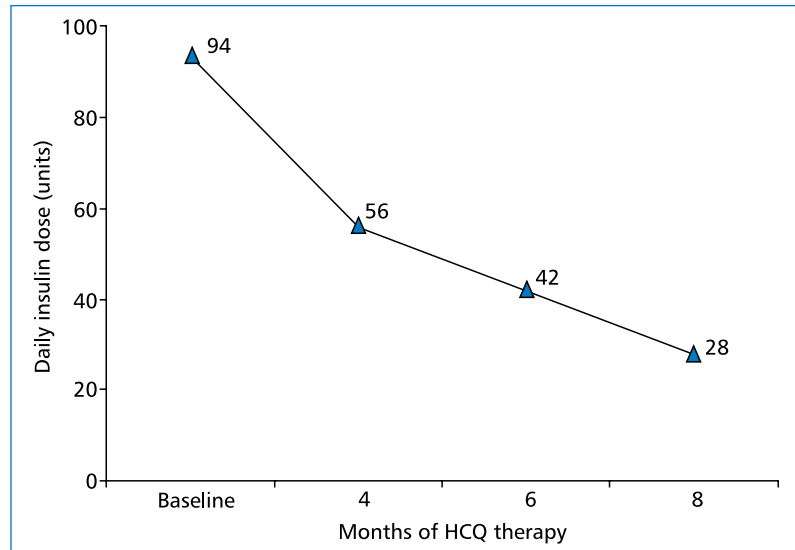


Figure 1. Daily insulin dose requirement (Y axis) by months of HCQ therapy (X axis)

Hydroxychloroquine works through a novel mechanism and may therefore be a useful adjunctive therapy for patients with T2DM [2]. In the current case its use as an add on antidiabetic drugs resulted in achievement of target HbA_{1c} level along with the control of plasma glucose levels. HbA_{1c} level decreased by 1.6% and FPG and PPG levels decreased by 69 mg/dL and 92 mg/dL respectively after HCQ was added to the treatment regimen. Due to glycemic control the daily insulin dose could be reduced by 66 units. Thus there was a 70% reduction in daily insulin dose requirement.

A recently conducted retrospective cohort study showed that use of HCQ was associated with 72% cardiovascular (CV) disease risk reduction in RA patients. The hazard ratio was 0.28 ($p = 0.002$) for CV disease events and 0.30 ($p = 0.004$) for composite coronary artery disease, stroke, and transient ischemic attack for HCQ users versus nonusers respectively [5]. The cardiovascular risk may also be diminished by HCQ due to beneficial lipid lowering, antiplatelet and antithrombotic effects [6].

Hydroxychloroquine is generally considered to be a very safe medication. The major safety concern with long-term HCQ use is retinopathy, the incidence of which according to the American Academy of Ophthalmology can be minimized by keeping the daily dose < 6.5 mg/kg/day [7].

Conclusion

Hydroxychloroquine should be considered as a therapeutic option in the refractory diabetic patients, since glycemic control is achieved through inhibition of insulin

degradation and improvement of insulin sensitivity. This case report illustrates the need for clinicians to have a heightened awareness about the antidiabetic effect of HCQ. Anti-inflammatory action, cholesterol and triglyceride lowering effect, antiplatelet and antithrombotic actions of HCQ may lower the cardiovascular risk. But such an overwhelming response of HCQ on metabolic parameters cannot be expected in every individual.

Conflict of interest

Dr. Mahesh Vasant Abhyankar and Dr. Suraj Atmaram Ghag are employees at IPCA Laboratories Limited Mumbai.

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