Hydroxychloroquine in Decompensated, Treatment-Refractory Noninsulin-Dependent Diabetes Mellitus

A New Job for an Old Drug?

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Study Objective: To evaluate the usefulness and safety of hydroxychloroquine in patients with decompensated, treatment-refractory noninsulin-dependent diabetes mellitus.

Design: Prospective, randomized, placebo, double-blind 6-month trial.

Patients: Thirty-eight patients with noninsulin-dependent diabetes resistant to commonly used therapies (oral drugs, insulin, combination of insulin and oral drugs).

Interventions: Two study groups: one received insulin ($n = 22$) and the other, glibenclamide ($n = 16$). In each group, half of the patients were randomly allocated into two subgroups who continued the previous treatment but took either placebo tablets or hydroxychloroquine, 200 mg three times a day. The four subgroups were as follows: insulin and placebo ($n = 11$); insulin and hydroxychloroquine ($n = 11$); glibenclamide and placebo ($n = 8$); and glibenclamide and hydroxychloroquine ($n = 8$).

Measurements and Main Results: At 6 months, relevant and statistically significant improvement occurred in the 11 patients who received the insulin and hydroxychloroquine (glucose profile decrease, −11.7 mmol/L; 95% CI, −13.9 to −9.5, $P = 0.001$; glycated hemoglobin A1c decrease, −3.3%; 95% CI, −3.9 to −2.7, $P = 0.001$). No significant changes were seen in patients on placebo. The daily insulin dose in patients treated with the combined insulin and hydroxychloroquine therapy had to be reduced an average of 30%. No important side effects were detected.

Conclusions: Combining antidiabetic therapy with hydroxychloroquine in decompensated, treatment-refractory patients with noninsulin-dependent diabetes may help to break the vicious circle of hyperglycemia and lead to better management of the disease.

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Insulin resistance is commonly, if not always, found in patients with noninsulin-dependent diabetes and has been attributed to defects in insulin actions (mainly postreceptorial) (1, 2). We (3) and others (4) have recently shown that chloroquine has some beneficial effects, apparently related to the severity of disease, on glucose homeostasis in a limited series of patients suffering from noninsulin-dependent diabetes.

The mechanism or mechanisms underlying the effect of chloroquine is still debated: in vitro, the drug inhibits insulin degradation in the rat liver (5), which theoretically may result in more insulin being released at posthepatic level; in vivo, insulin must be present, either administered therapeutically or secreted endogenously for chloroquine to be effective (3).

To evaluate hydroxychloroquine, a safer drug than chloroquine, in decompensated, treatment-refractory noninsulin-dependent diabetic patients, we used hydroxychloroquine (600 mg/d) in association with insulin or glibenclamide in a prospective 6-month, randomized, double-blind trial. Hydroxychloroquine reduced the total dose of insulin needed to reach diabetic control. Drug-related toxicity (retinopathy) was not found at the end of the study.

Patients and Methods

Study Population

Forty-eight diabetic patients (referred inpatients at the Diabetic Clinic Casa di Cura S. Rita, Taranto, Italy) gave informed consent to participate in our study after a clear and detailed explanation of its experimental nature. The study was carried out in accordance with the Helsinki Declaration II and was approved by the ethical committee of our institution. The patients, who had noninsulin-dependent diabetes, were decompensated despite different therapies: oral hypoglycemic agents at the maximal doses allowed, insulin, or combined insulin plus oral drugs. To take part in the study, the diabetic patients had to be under 70 years of age and without serious complications (hepatic, renal, or cardiac) or serious retinopathy.

The diabetic patients (10 men and 38 women) had the following characteristics: they were slightly overweight (mean body mass index, 27.9 ± 3.2 [±SD]; range, 24 to 28) and ranged in age from 33 to 70 years (mean age, 57 years ± 11.2); the duration of known disease ranged from 4 to 25 years (mean, 11.1 ± 8.4 years). Of the 48 patients, 31 were on an intensified insulin regimen because they had not responded to previous oral therapy; 16 of these patients were being treated with a combined insulin and sulfonylurea therapy according to the protocol we previously developed (6, 7). For most patients, the insulin regimen consisted of three spaced injections with a mixture of human regular and lente insulins at breakfast (40%

Table 1. *Characteristics of Diabetic Patients Treated with Insulin or Glibenclamide and Assigned to Placebo or Hydroxychloroquine Therapy**

Characteristics	Insulin-Treated		Glibenclamide-Treated	
	Placebo (n = 11)	Hydroxychloroquine (n = 11)	Placebo (n = 8)	Hydroxychloroquine (n = 11)
Age, *y*	58 ± 5.6	57 ± 5.3	57 ± 3.4	58 ± 2.9
Body mass index	27.8 ± 1.9	27.6 ± 2.3	27.9 ± 1.4	28.1 ± 1.7
Duration of known disease, *y*	11.2 ± 3.6	10.9 ± 3.3	11.1 ± 3	11.3 ± 2.8
Glycemic profile, *mmol/L*	20.5 ± 1.3	21.3 ± 1.6	20.3 ± 0.6	20.7 ± 0.6
Glycated hemoglobin A1c, %	12.1 ± 3.36	12.5 ± 1.98	12.5 ± 2.83	12.0 ± 1.4
C-peptide, *ng/mL*†	1.6 ± 0.6	1.7 ± 0.6	1.6 ± 2.2	1.6 ± 1.1

* Data are given as mean ± SD.
† To convert C-peptide values to pmol/L, multiply by 331.

of the total daily insulin dose), regular insulin at lunch (25% of the total dose), and another mixture of regular and lente insulins at dinner (35% of the total dose). In a few patients (4), we used a protocol that consisted of three injections of human regular insulin at meals and an ultralente or lente preparation at bedtime. In each case, the total daily insulin dose was over 100 units (range, 101 to 125 units). The remaining 17 patients received the maximal dose of oral drugs because they refused insulin therapy. All 48 patients had high levels of glycated hemoglobin A1c (HbA1c, 12.5% ± 7%), but no tendency to ketosis; the fasting C-peptide concentration was 1.6 ± 1.4 ng/mL (range, 0.3 to 2.5 ng/mL). Before entering the study, all patients were seen weekly for 2 consecutive months to try to obtain better glycemic control by changing the dose and type of insulin or oral agent administered. Ten patients responded favorably; their HbA1c levels dropped below 10% after the observation period.

Study Design

The remaining 38 diabetic patients had little or no improvement at the end of the observation period and entered the study. They were divided into two groups according to the treatment they were already on: one group (22 patients) was receiving insulin (Actrapid HM and Monotard HM, NOVO Industries, Copenhagen, Denmark) at a dose ranging from 70 to 110 U/d (mean, 95 ± 2 U/d [SE]) in three spaced doses with the modalities as stated previously; the other group (16 patients) was receiving glibenclamide.

The 22 insulin-treated diabetic patients were allocated randomly into two groups, each consisting of 11 patients: one group (insulin and placebo) continued the intensified insulin treatment whereas the other (insulin and treatment) received insulin and hydroxychloroquine. A double-blind procedure was used; patients received a placebo or hydroxychloroquine. The two groups were comparable with regard to age, duration of diabetes, and metabolic indexes (Table 1).

The 16 patients treated with glibenclamide were also allocated randomly into two groups, each consisting of 8 patients: one group was being treated with glibenclamide (5 mg three times a day) and placebo whereas the other received the glibenclamide dose (5 mg three times a day) and hydroxychloroquine (200 mg three times a day). The principles of the double-blind procedure were also followed. The two groups were comparable with regard to age, duration of known disease, and metabolic indexes (Table 1).

After an inpatient period of 6 weeks, during which basal variables were measured (diurnal glucose profile, HbA1c, endogenous secretory insulin reserve), outpatient control was assessed monthly for the next 6 months. Some metabolic variables were measured monthly (glucose profile and HbA1c) whereas beta-cell function and insulin sensitivity were studied in the basal state and at the end of the study. To avoid possible effects of caloric restriction, diabetic patients were also asked to maintain their usual diet (50% to 55% carbohydrate, 18% to 23% protein, and 27% to 32% lipid) and to avoid weight loss. Those patients who were taking medications other than antidiabetic drugs before entering the study continued the previous treatment during the trial. All patients were seen by an ophthalmologist in the basal state and every third month to detect possible retinal damages associated with hydroxychloroquine treatment.

Laboratory Methods

The diurnal plasma glucose profile represents the mean of the plasma glucose values measured every 2 hours during the day and every 4 hours during the night. The plasma C-peptide response to 1 mg glucagon given intravenously (Glucagon, NOVO Industries, Copenhagen, Denmark) was calculated as the C-peptide area above fasting by triangulation (time, 0 to 120 min). Blood samples were taken in the basal state and at 15-minute intervals for the first hour and at 30-minute intervals for the second hour. Blood specimens were collected in prechilled tubes containing 1.2 mg EDTA and 1000 units aprotinin (Trasylol, Bayer, Italy) per mL of blood. The intravenous insulin test was done by injecting intravenously 0.1 U/kg body weight of human regular insulin (Actrapid HM, NOVO Industries, Copenhagen, Denmark) and taking blood samples at 10-minute intervals for 2 consecutive hours. Plasma glucose was measured with a glucose-oxidase method on a Beckman glucose analyzer; glycated hemoglobin was measured by column chromatography (Auto A1c Analyzer, Kogaku Kioto, Menarini Diagnostici, Italy); plasma C-peptide was determined by radioimmunoassay as previously described (8). The interassay coefficient of variation of this method was 6.5% and the sensitivity limit was less than 0.1 ng/mL.

Statistical Analysis

Mean values and 95% confidence intervals (CIs) were determined for laboratory data. Results were statistically analyzed using paired and unpaired *t*-tests to compare laboratory data for subgroups of patients after 6 months of therapy.

Results

The addition of hydroxychloroquine to insulin therapy caused a significant decrease in the glucose profile and HbA1c in the 11 patients investigated, which was evident after 2 weeks of treatment and persisted until the sixth month (Table 2). In all diabetic patients in this group, both the fasting and glucagon-stimulated C-peptide area remained unchanged after therapy. Because the glycemic profile significantly improved, the daily insulin dose had to be reduced by approximately 30% (Table 2).

Patients treated with a combination of glibenclamide and hydroxychloroquine showed a significant reduction of both the glucose profile and HbA1c levels. The improvement of plasma glucose was evident after 10 days of treatment and persisted until the sixth month (Table 2). Fasting and glucagon-stimulated C-peptide levels did not show any significant change after therapy (Table 2).

During the insulin test, basal glucose levels remained

Table 2. *Laboratory Results of Patients with Noninsulin-Dependent Diabetes Mellitus Treated with Insulin or Glibenclamide at Baseline and 6 Months after Random Assignment to Placebo or Hydroxychloroquine Therapy**

Result	Insulin-Treated		Glibenclamide-Treated	
	Baseline (n = 11)	6-Month Change (n = 11)	Baseline (n = 8)	6-Month Change (n = 8)
Glycemic profile, *mmol/L*				
placebo	20.5 (19 to 22)	−0.9 (−1.9 to 0.1)	20.2 (19 to 21.4)	−0.3 (−0.7 to 0.1)
hydroxychloroquine	21.6 (20 to 23.2)	−11.7 (−13.9 to −9.5)	21.5 (20 to 23)	−10.8 (−12.7 to 8.9)
Glycated hemoglobin Alc, %				
placebo	12.1 (11.1 to 13.2)	−0.3 (−0.7 to 0.1)	12.5 (11.1 to 13.9)	−0.4 (−0.8 to 0)
hydroxychloroquine	12.2 (11 to 13.4)	−3.3 (−3.6 to −3)	12.1 (11 to 13.2)	−3.3 (−3.9 to −2.7)
C-peptide area, *ng/mL*				
placebo	25 (18 to 32)	−1 (−3 to 1)	23 (16.9 to 29.1)	−1 (−2.4 to 0.4)
hydroxychloroquine	22 (16.5 to 27.5)	−1 (−2.5 to 0.5)	22 (17.2 to 26.8)	0 (−0.9 to 0.9)
Insulin dose, *U/d*				
placebo	90 (80 to 100)	1 (−1.5 to 3.5)		
hydroxychloroquine	93 (83 to 103)	−24 (−30 to −17.9)		

* Numbers in parentheses represent the 95% CI.

stable for 20 minutes before insulin administration. In the basal state, the diabetics in the two placebo groups showed only minimal changes from the basal glucose levels after receiving insulin (the mean [±SE] percent decrease from baseline was −8.6% ± 3.2% in the insulin and placebo group and −20.2% ± 6% in the glibenclamide and placebo group), which remained unchanged after the second insulin test given at the end of the study period (−9.5% ± 3.1% in the insulin and placebo group and −19.8% ± 6.5% in the glibenclamide and placebo group, P = 0.2). After 6 months of treatment, the percent glycemic decrease after the insulin sensitivity test in patients in the two treatment groups was significantly higher than that seen in the basal state (insulin and treatment group: basal, −9.2% ± 3.2%; post-treatment, −23% ± 6.4%; P = 0.04; glibenclamide and treatment group: basal, −22.9% ± 3.7%; post-treatment, −45.2% ± 8.5%; P = 0.04).

The improvement of both the glucose profile and HbA1c seen in treated patients was not found in patients taking placebo (Table 2). The weight of all patients remained stable during the study period.

Except for epigastric ache that disappeared with antiacids, no side effects were reported during treatment with hydroxychloroquine. One patient treated with the combined insulin and hydroxychloroquine had severe hypoglycemia after 2 months of treatment, and it was necessary to reduce the daily insulin dose drastically. Another patient showed a worsening of pre-existing alopecia. In the ophthalmoscopic examinations (basal, third and sixth month), no retinal alterations were seen in diabetics receiving hydroxychloroquine apart from pre-existing retinopathy that remained unchanged.

Discussion

Hydroxychloroquine exerts a positive effect on glycemic control in patients with noninsulin-dependent diabetes resistant to commonly used therapies (oral antidiabetic drugs, insulin, and combination of insulin and oral agents). The clinical and metabolic characteristics of these patients are akin to those secondarily resistant to oral drugs: this condition is thought to occur in 20% to 30% of patients with noninsulin-dependent diabetes (9), but its pathogenesis is far from being elucidated (10, 11). The diabetic patients taking part in our study showed a residual beta-cell function but could not improve their metabolic control despite intensified therapy, dietary compliance, and absence of causes responsible for metabolic decompensation. On the other hand, these patients certainly were insulin resistant; the insulin sensitivity test showed only minimal, if any, decrease of plasma glucose concentrations.

The encouraging, although limited, findings (3, 4) about the beneficial effect of chloroquine to improve glycemic control in a few patients with noninsulin-dependent diabetes and the reported hypoglycemic reactions following antimalarial therapy with the drug (12) prompted us to begin a clinical trial with hydroxychloroquine, a safer drug than chloroquine, in decompensated diabetic patients. The improvement of glycemic control we observed in our patients taking hydroxychloroquine does not appear to be related to amelioration of insulin secretion, because both fasting and glucagon-stimulated C-peptide levels remained unchanged after 6 months of treatment. C-peptide is secreted along with insulin from the pancreatic beta-cells and represents a good index of insulin secretion because unlike insulin it is not degraded by the liver (13). When they did oral glucose tolerance tests in six patients with mild noninsulin-dependent diabetes, Smith and colleagues (4) observed that a 2.5 day treatment with chloroquine improved glucose tolerance without changing C-peptide concentrations. On the other hand, insulin plasma levels were higher after chloroquine administration, which led

the authors to hypothesize that the drug might have changed the intrahepatic clearance of insulin. It must be recalled, however, that the beta-cell secretory activity was evaluated at different plasma glucose levels (before and after treatment) so that the possibility that any eventual positive effect of both chloroquine and hydroxychloroquine on insulin secretion might have been masked by the reduced post-treatment glucose levels must be considered. Much evidence indicates that the prevailing plasma glucose level is essential in the control of insulin release in both normal subjects and patients with non-insulin-dependent diabetes mellitus (14, 15).

The mechanism responsible for the beneficial effect of this class of compound on glucose homeostasis is still obscure. Studies in vitro suggest that chloroquine may inhibit insulin degradation at a postreceptorial level, thus enhancing the metabolic effects of the hormone (16, 17), as well as accelerate insulin-stimulated glucose transport (18). The insulin resistance found in patients with noninsulin-dependent diabetes has been attributed to both receptor and postreceptor defects. Arner and colleagues (19), however, have recently challenged this assumption by demonstrating normal insulin binding to hepatic membranes isolated from diabetic patients. Thus, the current opinion is that a postbinding defect in insulin action must be responsible for the observed insulin resistance in patients with well-established hyperglycemia.

Although the insulin test represents only a rough estimate of insulin sensitivity, it nonetheless may give some measure of the general responsiveness to the hormone in responders' tissues, mainly muscle, because insulin is given in systemic circulation; evidence indicates that in the insulin-stimulated state, muscle is the primary tissue responsible for the insulin resistance (2). Thus, increased glucose utilization in periphery may account for the beneficial effect of chloroquine and hydroxychloroquine in glucose homeostasis of diabetic patients, although a simultaneous effect at the hepatic level (that is, suppression of gluconeogenesis) cannot be excluded. Additional studies with more sophisticated techniques (euglycemic clamp with glucose turnover) will help to clarify this important issue.

Although the clinical and laboratory data of this study seem encouraging, additional follow-up is indicated in order to evaluate the long-term effectiveness and the safety of hydroxychloroquine. With regard to the first question, Svenson and colleagues (20) found only transitory benefits of chloroquine on glucose tolerance in seven patients suffering from rheumatoid arthritis but hydroxychloroquine was never assessed. With regard to possible side effects, ophthalmoscopic examination (and in some cases fluorangiography) did not show any variation of the retinal status at the end of the our study, which agrees with the data of Johnson and Wine (21), who showed that massive doses of hydroxychloroquine for a long period did not cause retinal toxicity. We think, however, that some precautions, such as avoiding treatment in patients with severe retinopathy, are necessary.

Although more studies are needed to confirm the long-term safety and usefulness of hydroxychloroquine, we think that a trial with the drug should be done in decompensated patients with noninsulin-dependent diabetes resistant to commonly used therapies, to reduce fasting hyperglycemia, which is "toxic" for both insulin secretion and action (22).

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References

1. **Kahn CR.** Insulin resistance: a common feature of diabetes mellitus. *N Engl J Med.* 1986;**315**:252-4.
2. **DeFronzo RA.** The triumvirate: beta-cell, muscle and liver. A collusion responsible for NIDDM. *Diabetes.* 1988;**37**:667-87.
3. **Quatraro A, Consoli G, Ceriello A, Giugliano D.** Is there a role for chloroquine treatment in diabetes? A three case report [Letter]. *Diabete Metab.* 1988;**14**:666-7.
4. **Smith GD, Amos TA, Mahler R, Peters TJ.** Effect of chloroquine on insulin and glucose homeostasis in normal subjects and in patients with non-insulin-dependent diabetes mellitus. *Br Med J [Clin Res].* 1987;**294**:465-7.
5. **Dennis PA, Aronson NN Jr.** The effects of low temperature and chloroquine on 125I-insulin degradation by the perfused rat liver. *Arch Biochem Biophys.* 1981;**212**:170-6.
6. **Quatraro A, Consoli G, Minei A, Ceriello A, Giugliano D.** Aggiornamenti in tema di terapia insulinica. *Boll Acc Med Pistoiese F Pacini.* 1985;**54**:109-33.
7. **Quatraro A, Consoli G, Ceriello A, Giugliano D.** Combined insulin and sulfonylurea therapy in non-insulin-dependent diabetics with secondary failure to oral drugs: a one year follow-up. *Diabete Metab.* 1986;**12**:315-8.
8. **Giugliano D, Cozzolino D, Salvatore T, et al.** Altered metabolic and hormonal responses to epinephrine and beta-endorphin in human obesity. *J Clin Endocrinol Metab.* 1988;**67**:238-44.
9. **Camerini-Davalos RA, Marble A.** Incidence and causes of secondary failure in treatment with tolbutamide: experience with 2500 patients treated up to 5 years. *JAMA.* 1962;**181**:1-4.
10. **Groop L, Pelkonen R.** Treatment failures: a common problem in the management of patients with type-2 diabetes. *Acta Endocrinol (Copenh).* 1984;**105**(Suppl 262):131-5.
11. **Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D.** Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. *Diabetes Care.* 1986;**9**:129-33.
12. **Bamber MG, Redapth A.** Chloroquine and hypoglycaemia [Letter]. *Lancet.* 1987;**1**:1211.
13. **Polonsky KS, Rubenstein AH.** C-peptide as a measure of secretion and hepatic extraction of insulin. Pitfalls and limitations. *Diabetes.* 1984;**33**:486-94.
14. **Giugliano D, Ceriello A, Saccomanno F, Quatraro A, Paolisso G, D'Onofrio F.** Effects of salicylate, tolbutamide, and prostaglandin E2 on insulin responses to glucose in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab.* 1985;**61**:160-6.
15. **Giugliano D, Di Pinto P, Ceriello A, et al.** Glycemic control with an artificial pancreas improves insulin responses to both oral and i.v. glucose in nonobese noninsulin-dependent diabetic subjects. *Acta Diabetol Lat.* 1985;**22**:203–13.
16. **Fyles JM, Cawthorne MA, Howell SL.** The effect of chloroquine on receptor internalization in pancreatic islets. *Diabetic Med.* 1986; **3**:P57, 373A.
17. **Opara E, van Haeften T.** Use of chloroquine in adipocyte insulin binding experiments: improved estimation of insulin internalization and receptor bound insulin with linearization of the Scatchard plot [Abstract]. *Diabetes.* 1987;**26**(Suppl 1):160A.
18. **Cynober L, Aussel C, Vaubordolle M, Agneray J, Ekindjian OG.** Modulation of insulin action on 2-deoxyglucose uptake by chloroquine in chick embryo fibroblasts. *Diabetes.* 1987;**36**:27-32.
19. **Arner P, Einarsson K, Ewerth S, Livingston J.** Studies on the human liver insulin receptor in noninsulin-dependent diabetes mellitus. *J Clin Invest.* 1986;**77**:1716-8.
20. **Svenson KL, Lundqvist G, Wide L, Hallgren R.** Impaired glucose handling in active rheumatoid arthritis: effects of corticosteroids and antirheumatic treatment. *Metabolism.* 1987;**36**:944-8.
21. **Johnson MW, Wine AK.** Hydroxychloroquine therapy in massive total doses without retinal toxicity. *Am J Ophthalmol.* 1987;**104**: 139-44.
22. **Unger RH, Grundy S.** Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. *Diabetologia.* 1985; **28**:119-21.