

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma

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Background: Although antiinflammatory therapy is accepted as the cornerstone of asthma treatment, available systemic immunosuppressive agents are not widely used because of justified concerns over potential toxicity. Hydroxychloroquine (HCQ) is a well-tolerated, safe immunomodulating drug, with proven efficacy in rheumatic diseases and known actions that suggest potential utility in the treatment of asthma.

Objective: We sought to assess the effectiveness of HCQ in subjects with moderate symptomatic asthma.

Methods: Symptomatic asthmatic subjects receiving stable doses of at least 6 puffs of inhaled corticosteroid per day with daily need for β_2 -adrenergic agonists were studied. After baseline run-in, these subjects were randomized to 30 weeks of HCQ ($n = 8$) or placebo ($n = 9$). Objective measures included change from baseline mean FEV₁, morning and evening peak flows, β_2 -agonist use, IgE level, and need for rescue corticosteroids. Subjective symptom scores from bidaily diaries were also obtained.

Results: In the treatment group, mean FEV₁ at the last 2 visits on therapy increased by 10.8% ($P < .05$), morning peak flows rose 16.2% ($P < .03$), evening peak flows rose 14.2% ($P < .04$), and β_2 -agonist use fell 18.6% ($P < .03$). Mean IgE level declined 48% from 240 to 125 IU/mL ($P < .05$). In the placebo group no significant change in these parameters occurred. Comparison of changes in these objective measures between the treatment and placebo groups failed to reach significance in the small population studied. Corticosteroid rescue interventions were required in 4 patients receiving placebo and 2 receiving HCQ. HCQ was well tolerated without notable side effects.

Conclusions: Although the size of our sample population precludes definitive conclusions, these findings extend previous open-label observations. The late improvement in the HCQ group is consistent with its known slow onset of action. Further studies are warranted to confirm the antiasthmatic and antiallergic effects of HCQ and to investigate its potential as a disease-modifying agent. (*J Allergy Clin Immunol* 1998;102:198-203).

Key words: Asthma, IgE, hydroxychloroquine, antiinflammatory agents, asthma therapy, antimalarial

Abbreviations used

HCQ: Hydroxychloroquine

PEFR: Peak expiratory flow rate

Bronchial asthma is one of the most common chronic illnesses, affecting more than 5% of the population.¹ Both its prevalence and its severity, particularly in terms of mortality statistics, appear to be rising in industrialized Western countries. Epidemiologic and histopathologic studies complement convincing pathophysiologic evidence for the participation of a variety of inflammatory mediators and cells in an ongoing inflammatory process and support the view that asthma results from a chronic inflammatory stimulus acting on the substrate of innate bronchial hyperreactivity.

The shortcomings of currently available asthma therapy are many: symptom control is frequently inadequate; chronic, even indefinite therapy is required due to disease flare on cessation^{2,3}; and, perhaps most disappointingly, in some patients asthma seems to progress despite regular treatment.⁴ For this reason, clinical studies have investigated the potential utility of more potent immunosuppressive treatments, including methotrexate,⁵⁻¹⁰ gold salts,¹¹⁻¹³ cyclosporine,^{14,15} dapsone,¹⁶ and intravenous immunoglobulin¹⁷ during the last decade. Despite the differences among these agents, multiple trials have demonstrated a notably consistent oral corticosteroid-sparing effect (ranging from 40% to 70%) but at the same time have highlighted the considerable limitations of this group of drugs. Frequent significant and even fatal side effects necessitate careful monitoring, add cost, and indicate that their use must be confined to oral corticosteroid-dependent asthmatic subjects. Moreover, efficacy in clinical trials has been assessed only in terms of their corticosteroid-sparing effect. Perhaps because of the confounding influence of the concomitant corticosteroid taper, proof of antiasthmatic effects as shown by conventional parameters, such as increases in spirometric or peak flow measurements, are generally lacking.

Hydroxychloroquine (HCQ) is an antiasthmatic agent commonly used as a primary disease-modifying therapy for such diseases as rheumatoid arthritis and lupus erythematosus. As compared with other available agents, its remarkably benign toxicity profile¹⁸⁻²¹ recommends con-

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sideration for use in non-oral steroid-dependent asthmatic subjects. We have previously reported on extensive open-label trials of HCQ that strongly suggested a consistent antiasthmatic and antiallergic drug effect.²²⁻²⁵ We now report the results of a double-blind, placebo-controlled trial of HCQ in subjects with moderate symptomatic asthma.

METHODS

Between March 1994 and May 1995, sixty-three symptomatic asthmatic subjects between ages 18 to 65 years who met standard historical criteria for the diagnosis of asthma were recruited from an office practice and from media advertisements and screened for entry into a 30-week double-blind, placebo-controlled study approved and supervised by the Columbia Hospital Investigational Review Board (Milwaukee, Wis). All were receiving stable doses of inhaled corticosteroids of at least 6 puffs/day and were using daily β -adrenergic agonists for symptom relief. Nineteen volunteers satisfied entry requirements, which included (1) a baseline FEV₁ value between 40% to 85% with an increase of at least 15% of actual value after 2 puffs of albuterol from a metered-dose inhaler and (2) the presence of significant symptoms as documented on a daily diary card during the 2 weeks before the second visit. Before randomization to the study drug, all volunteers demonstrated acceptable baseline ophthalmologic and physical examination findings, as well as complete blood counts, blood chemistry, fasting cholesterol and lipid profiles, theophylline levels, chest x-ray, and EKG studies. Sera for baseline IgG, IgA, IgM, and IgE levels were drawn and stored for analysis after the study was complete.

To reach acceptable dosage levels (<6.5 mg/kg/day) with HCQ 200 mg caplets, doses were adjusted according to baseline weights, and volunteers under 90 lbs or over 275 lbs were excluded. All entered patients had not received any oral or parenteral corticosteroids within the 6 weeks before entry, were presently nonsmokers with less than 20 pack-years of cigarette consumption, and were in otherwise good health with no history of significant ocular disease, psoriasis, porphyria, G-6-PD deficiency, acute sinusitis, allergic bronchopulmonary aspergillosis, interstitial lung disease, tuberculosis, or any other infectious disease or malignancy. No volunteers were receiving systemic hyposensitization therapy.

Safety monitoring included repeat complete blood count, chemistry, fasting cholesterol and lipid profiles, and theophylline levels obtained midway and at the end of study. Ophthalmologic exams were repeated at 12 and 24 weeks, as well as at study exit. Sera for repeat quantitative IgG, IgA, IgM, and IgE levels were obtained midway and at the end of study and stored at -30° C, and levels were determined after study completion.

Objective efficacy variables included the following: (1) change in mean FEV₁ from baseline, (2) change in average morning and evening prebronchodilator peak flows (2-week mean), (3) change in bronchodilator use (2-week mean), and (4) frequency of rescue interventions with oral corticosteroids. Changes in serum IgE, cholesterol, and lipid profiles were also assessed. Subjective measures of evaluation included symptom scores for the following: (1) wheezing, chest tightness, and/or breathlessness (0 = absent, 1 = mild, 2 = moderate, and 3 = severe); (2) perceived need for bronchodilator at 6 hours (0 = absent, 1 = mild, 2 = definite need, and 3 = unable to go beyond 6 hours); and (3) nocturnal asthma (0 = slept well, 1 = slight wheezing or tightness, 2 = awakened by asthma or unable to sleep, and 3 = awakened several times or awake much of the night because of asthma).

The trial was divided into a 6-week run-in period followed by 30 weeks of active treatment with study medications. Spirometry was

TABLE I. Baseline demographic data

	HCQ (n = 8)	Placebo (n = 9)
Sex	6 M/2 F	7 M/2 F
Age*	37.9 ± 4.0	44.7 ± 5.1
Mean duration of asthma (yrs)*	12.9 ± 1.5	10.9 ± 1.9
No. hospital and emergency department visits prior year*	None	0.6 ± 0.2
Micrograms of inhaled corticosteroids/day*	464 ± 140	499 ± 109
Atopic (positive skin test responses)	8/8	7/8

*Mean ± SEM.

obtained 3 times during baseline (at entry visit and at weeks 3 and 6). Subjects were randomized only if all 3 FEV₁ measurements met criteria, if diary card criteria were met, and if laboratory evaluation was acceptable. Follow-up spirometry studies were performed every 6 weeks. Peak flow readings (best of 3 attempts) were obtained in the morning and evening before and after inhaled bronchodilator administration. Study subjects with more severe symptoms were given oral steroid corticosteroid rescue medication on a standard schedule. Data obtained during the 6 weeks after administration of oral steroids was not included in summary data.

Statistical analysis made use of Wilcoxon signed-rank tests for intragroup comparisons and Mann-Whitney tests for between-group comparisons by using Statview 4.5 (Abacus Concepts Inc, Berkeley, Calif). The means of the 3 initial spirometric studies and the mean of the first 6 weeks of peak flow and bronchodilator use diary data were used as baseline values. The mean of the last 2 spirometric flow study measurements and last 6 weeks of peak flow and bronchodilator use data are included in the statistical analysis for all patients who completed at least 16 weeks in the study.

RESULTS

The study drug was well tolerated, with no significant adverse events reported. A total of 4 volunteers did not complete the study. One control volunteer was terminated before randomization after discovery of a breast malignancy, and another exited at 18 weeks because of worsening asthma. One treatment group volunteer was terminated due to lack of compliance 6 weeks after randomization, and another was lost to follow-up at week 24. During the course of the study, only 2 patients receiving HCQ, as opposed to 4 patients receiving placebo, required an oral burst of corticosteroid as rescue medication. No significant change in theophylline level occurred in the single treatment group volunteer maintained on this drug during the trial.

Comparisons between the groups revealed no significant differences in age, gender composition, duration of asthma, and atopy (Table I). The control group showed a slightly higher number of hospital visits, emergency department visits, or both in the prior year. However, there were no significant differences in multiple measures of baseline pulmonary status or in perceptions of asthma symptom severity (Table II). Average daily bronchodilator use was significantly greater in the HCQ group; however, this difference was not reflected in the baseline symptom score.

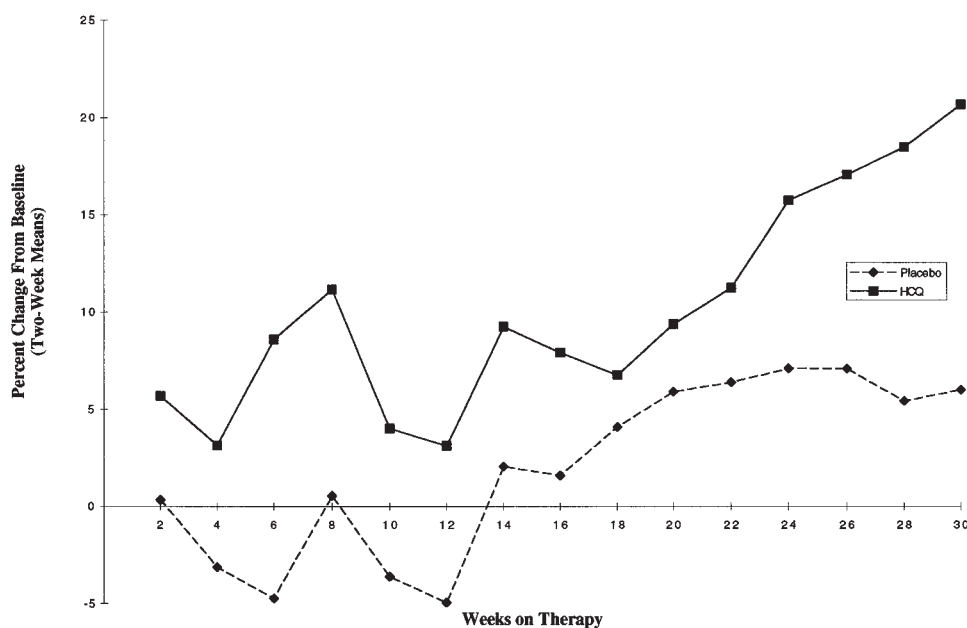


FIG. 1. Changes in morning PEFR.

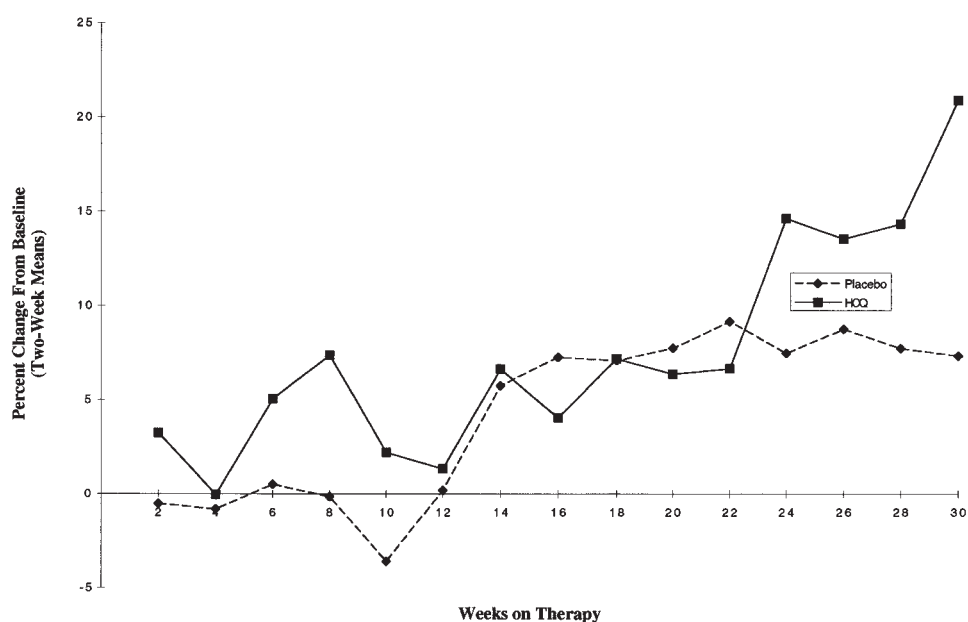


FIG. 2. Changes in evening PEFR.

As shown in Table III, in the HCQ group the mean FEV_1 at the last 2 visits improved significantly over the mean of 3 baseline findings by 11.2% (2.23 to 2.48 L/sec) as opposed to a lack of change seen in the placebo group. Similarly, comparisons of the means of the last 6 weeks' morning and evening peak flows and in β_2 -agonist use with the means of the baseline 6 weeks reveal statistically significant improvements. Peak flows rose a mean of 70 L/min (16.2%) in the morning and a mean of 68

L/min (14.2%) in the evening, whereas β_2 -agonist use decreased nearly 20%. Changes in morning and evening peak flow rates, viewed as a moving 2-week average, show an improvement occurring only after 4 months of therapy, which did not appear to plateau at trial end at week 30 (Figs. 1 and 2). In contrast, the placebo group demonstrated no significant change in any parameter. Although the percent fall in bronchodilator use in the study group did fall significantly as compared with the

TABLE II. Baseline pulmonary status

	HCQ	Placebo	P value
FEV ₁ (% predicted)	56.1 ± 0.04	59.3 ± 0.04	NS
FEV ₁ (L/sec)	2.23 ± 0.14	2.30 ± 0.21	NS
FVC (L)	3.66 ± 0.16	3.82 ± 0.26	NS
MMEF (L/sec)	1.38 ± 0.16	1.39 ± 0.22	NS
Morning PEFR (L/min)	430 ± 43	439 ± 53	NS
Evening PEFR (L/min)	479 ± 35	454 ± 55	NS
Bronchodilator use/day	5.9 ± 0.8	3.4 ± 0.6	<.02
Nocturnal symptom score	1.3 ± 0.2	1.5 ± 0.2	NS
Daytime symptom score	1.7 ± 0.1	1.8 ± 0.2	NS
Need for bronchodilator at 6 hours	2.1 ± 0.2	1.8 ± 0.2	NS

Values are mean ± SEM.

FVC, Forced vital capacity; MMEF, midmaximal expiratory flow rate; NS, not significant.

placebo group ($P < .05$), differences in bronchodilator use at study entrance may account for this finding. Comparisons of percent change in FEV₁ and peak flow rates in each of the 2 groups showed no significant differences.

Symptom scores did not vary significantly from baseline in either group (data not shown), primarily because of the small number of patients available for analysis who had mean symptom scores of 2 or greater (moderate severity) at baseline ($n \leq 5$ for any single symptom in either group).

Only the HCQ group demonstrated a statistically significant decrease in serum IgE (48%) and IgM (23%) levels; no corresponding alteration in IgG or IgA levels was found (Table IV). There was no significant difference in immunoglobulin levels or change in levels between the control and treatment groups. Although no subject had any significant infections or other adverse events, 1 volunteer did have an IgM level below normal range at study exit. Because quantitative immunoglobulin levels were run in batch only after the conclusion of the study, this finding was made only retrospectively; follow-up studies showed normalization of IgM levels.

The HCQ group also demonstrated statistically significant decreases in serum cholesterol (10%) and low-density lipids (14%), with apparent sparing of high-density lipid levels. No change was noted in the control group (Table V), and the changes in the treatment group as compared with the control group did not reach the level of significance.

DISCUSSION

Trials of immunosuppressive agents for asthma date to at least 50 years.¹³ Use of such approaches has been complicated by the occurrence of grave and even fatal side effects.¹⁴ As a consequence, their application has been confined to very severe, treatment-resistant, oral corticosteroid-dependent asthmatic subjects in whom drug responses appear to be attenuated and who thus may be a poor gauge of the potential benefits of systemic agents. For this reason, the safety profile of HCQ recommended its consideration in the treatment of symptomatic non-oral corticosteroid-dependent asthmatic subjects. To our knowledge, this is the first report describing a controlled trial of a systemic antiinflammatory agent in non-oral corticosteroid-dependent asthmatic subjects.

The range of actions ascribed to HCQ (or to related antimalarials) appears particularly relevant for application to asthma therapy. Antimalarials block histamine-induced bronchoconstriction in an animal model^{15,16} and reproducibly decrease antigen-induced bronchoconstriction in guinea pig trachea.¹⁷ The participation of IgE in the asthmatic inflammatory cascade is well accepted and has recently been suggested as being caused by upregulation of IgE.¹⁸ If so, the fact that antimalarials inhibit IL-4-driven IgE synthesis of human peripheral blood lymphocytes,¹⁹ abrogate antigen-presenting cell presentation of ragweed antigen in vitro,²⁰ and are associated with decreased circulating IgE levels in open-label observations¹² suggest that HCQ may decrease bronchial inflammation by reducing the IgE involved in its pathogenesis. HCQ and other antimalarials reduce neutrophil and peripheral blood monocyte superoxide production and release,²¹ stabilize lysosomal membranes,²² and decrease lysosomal enzyme activity in neutrophils,²³ raising the possibility that such effects extend to eosinophils and basophils, leukocytes critical to the pathogenesis of asthmatic inflammation. Additionally, antimalarial inhibition of replication and transmission of HIV,^{24,25} blockade of adenovirus and influenza transmission (Sperber, personal communication, 1993), and reduction of circulating intercellular adhesion molecule-1 levels²⁶ suggest that HCQ may limit the incidence or severity of viral infections, which frequently trigger asthmatic exacerbations.²⁷

The data presented confirm the antiallergic effects of HCQ in terms of modulation of circulating IgE levels. Mild effects on circulating IgA and IgG induced by HCQ have been previously reported²⁸ that are similar to those seen here with IgM. However, the findings presented herein, coupled with our previous observations, argue that HCQ appears to mediate a more selective and profound inhibition of IgE. In thirty-five patients studied in earlier open-label trials, mean IgE fell 41% after at least 6 months therapy (data not shown). The fact that significant change was seen only in the group of patients with elevated baseline levels of IgE suggests that HCQ, in contrast to conventional immunosuppressive agents, may act to modulate rather than suppress IgE levels. Whether this effect plays a role in the antiasthmatic actions of

TABLE III. Change in pulmonary functions and β_2 -agonist use

	HCQ (n = 8)			Placebo (n = 9)		
	Δ	% Δ	P value	Δ	% Δ	P value
FEV ₁ (L/sec)	0.25 $\pm$ 0.10	+11.2	<.05	-0.01 $\pm$ 0.12	-0.3	NS
Morning PEF (L/min)	69.5 $\pm$ 23.6	+16.2	<.03	20.9 $\pm$ 24.3	+4.8	NS
Evening PEF (L/min)	68.1 $\pm$ 25.0	+14.2	<.04	30.4 $\pm$ 19.7	+6.7	NS
MDI use/day	-1.1 $\pm$ 0.3	-18.9	<.04	-0.2 $\pm$ 0.5	-4.7	NS

Values are mean $\pm$ SEM.

MDI, Metered-dose inhaler; NS, not significant.

TABLE IV. Changes in immunoglobulin levels from baseline to study exit

	HCQ (n = 7)			Placebo (n = 7)		
	Baseline	% Δ	P value	Baseline	% Δ	P value
IgE (IU/mL)	240 $\pm$ 88	-48.1	<.05	291 $\pm$ 129	8.6	NS
IgG (mg/dL)	949 $\pm$ 96	-0.8	NS	1071 $\pm$ 56	-0.5	NS
IgA (mg/dL)	248 $\pm$ 40	-17.1	NS	278 $\pm$ 40	1.9	NS
IgM (mg/dL)	144 $\pm$ 29	-22.7	<.03	137 $\pm$ 19	-11.9	NS

Values are mean $\pm$ SEM.

NS, Not significant.

TABLE V. Changes in lipid levels from baseline to study exit

	Baseline	Δ	% Δ	P value
Cholesterol (n = 7)	238.6 $\pm$ 19.9	-22.7 $\pm$ 5.8	-9.5	<.02
HDL (n = 7)	41.6 $\pm$ 5.3	1.8 $\pm$ 1.1	4.5	NS
LDL (n = 6)	153.0 $\pm$ 13.0	-21.0 $\pm$ 3.1	-13.7	<.02
Triglycerides (n = 7)	266.6 $\pm$ 121.5	-35.1 $\pm$ 46.3	-13.2	NS

Values are mean $\pm$ SEM (mg/dL).

HDL, High-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

HCQ remains unclear, but recent reports demonstrating antiasthmatic effects of other therapies that lower IgE levels support this hypothesis.^{5,29}

Although the small numbers enrolled in this study preclude definitive conclusions, the increase in spirometric measurements and peak flows rate, as well as the decrease in use of rescue bronchodilator, are of both statistically significant and clinically relevant magnitude. Perhaps most persuasive that these findings are real and attributable to an underlying drug effect is the impressive rise in peak expiratory flow rate (PEFR) that begins only after about 20 weeks of therapy. The timing of this change not only strikingly parallels the delay in improvements seen in our earlier observations¹² but, moreover, is quite consistent with the known delayed response to HCQ in other illnesses. The lack of effect seen by Roberts et al³⁰ in an earlier 8-week trial is perhaps explained by this slow onset of action. Moreover, the fact that the increases in PEFR did not appear to reach a plateau at week 30 raises the possibility that a longer trial might have revealed additional benefit. The improvements in PEFR seen with the addition of HCQ to inhaled corticosteroids in this study compare favorably with those reported after the addition of a 5-lipoxygenase

inhibitor to patients receiving smaller doses of inhaled beclomethasone (70 L/min vs 24 L/min).³¹ Whether the long duration of prior asthma, averaging over 12 years in the HCQ group, may have also diminished responses to drug intervention is unknown.

Earlier reports of a hypocholesterolemic, hypolipoproteinemic effect of HCQ³² are corroborated by these observations. Although lack of dietary controls renders any conclusions as tentative, significant reductions in cholesterol (10%) and low-density lipoproteins (14%) coupled with relative sparing of high-density lipoproteins were observed only in the HCQ group. These findings are also in agreement with our experience in 15 patients receiving open-label treatment in whom comparable and statistically significant decreases in both cholesterol and low-density lipoproteins were seen after 6 months of therapy (data not shown).

Larger multicenter studies are needed to verify the utility of HCQ as an adjunctive or alternate antiasthmatic drug. Trials in asthma of more recent onset or milder severity may demonstrate similar disease-modifying effects as seen in rheumatic disease. In the interim it would appear prudent to consider use of HCQ as an antiasthmatic agent in selected refractory cases, especially in patients dependent on or requiring frequent bursts of oral corticosteroids.

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