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Hydroxychloroquine Blood Levels in SLE: Clarifying dosing controversies and improving adherence

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Abstract

OBJECTIVES—Hydroxychloroquine is used for its effect on systemic lupus erythematosus (SLE) disease activity and long-term benefits. This can be limited by adherence. One way to assess adherence is to measure blood levels. Conflicting data exist regarding blood levels and disease activity. There is dosing controversy; rheumatologists recommend weight-based, while ophthalmologists advocate height-based 'ideal body weight' dosing.

METHODS—Patients were prescribed hydroxychloroquine not to exceed 6.5mg/kg (max400mg/day). In hemodialysis, the dose was 200mg after each session, in renal insufficiency it was 200mg/day. Levels were measured at each visit with a therapeutic range of 500-2000 ng/ml. Patients were divided according to baseline blood level. To assess the impact of measurement and counseling on adherence, we compared the proportion of patients with a level of 500ng/ml or higher based on how many prior assessments the patient had.

RESULTS—The proportion of patients with hydroxychloroquine levels in the therapeutic range differed significantly by age, gender and vitamin D level. There was a trend toward lower levels with renal failure. Blood levels were similar regardless of height and ideal body weight. Comparing those with undetectable, sub-therapeutic and therapeutic levels, disease activity decreased (SLEDAI 2.92, 2.36 and 2.20)(P=0.04, for trend). At first, 56% were therapeutic and by the third measurement this increased to 80% (p =<0.0001).

CONCLUSION—There was a trend towards higher disease activity with lower hydroxychloroquine levels. Renal failure dosing led to sub-optimum levels. We show that weight-based dosing (max 400mg daily) is appropriate and that height does not appear to influence levels. Measurement, counseling and repeated testing can increase adherences rates.

INTRODUCTION

Hydroxychloroquine is the cornerstone of medical management of systemic lupus erythematosus (SLE). It has been shown to prevent flares (1), decrease thrombosis (2-5), improve lipids (6), and decrease insulin resistance (7-9). In terms of its specific effects in SLE, it is an effective means of treating cutaneous manifestations (10) and arthritis (11). It

has been shown to enhance response to other treatments in those with renal involvement (12). It associates with improved survival (3, 13) and decreased organ damage (14).

Medication non-adherence predicts poor outcomes in chronic diseases including SLE (15). The non-adherence rates in patients with SLE range from 3% to 76% depending on the methods used (16-20). Self-reported rates of non-adherence are between 7-45%(17, 18, 20-22). Koneru *et al* based their analysis on pharmacy refill information and found that 51% of individuals were non-adherent to their hydroxychloroquine at least 80% of the time (19). Ting *et al*(23) found that 29% of adolescents and young adults with SLE had undetectable hydroxychloroquine levels which correlated with refill rates obtained from pharmacies. SLE medication regimens are often changed and intensified in response to disease activity without knowing whether patients have been adherent to first line therapy. In this setting, any opportunity to gain knowledge regarding hydroxychloroquine adherence is likely to have clinical utility. It is unknown whether knowledge of a patient's blood levels of hydroxychloroquine coupled with counseling when the levels are low improves the rate of adherence.

Regarding hydroxychloroquine levels and lupus activity, Costedoat- Chalumeau *et al* (24) measured whole blood levels in 143 individuals taking a standard dose of 400 mg per day and found a lower hydroxychloroquine level in those with active disease and that lower baseline levels were predictive of disease flare. Francès *et al* (25) evaluated hydroxychloroquine levels in chronic discoid lupus and found that median blood hydroxychloroquine concentration was significantly higher in patients with complete remission compared with partial remission and treatment failure. However, even if a relationship between blood levels and flare was found, in a subsequent clinical trial, no reduction of flare was obtained when levels were increased to a target level of ≥1000ng/ml (26).

It is possible to measure plasma, serum and whole blood hydroxychloroquine levels. The measurement of whole blood rather than plasma hydroxychloroquine is important. Whole blood concentrations are approximately five times the plasma concentrations, are more precise, and are favored for pharmacokinetic measurements (27).

Here we report on the utility of blood hydroxychloroquine levels in clinical practice, their relationship to disease activity and other variables such as body mass index, height, renal function and ethnicity and the effect of measurement and counseling on subsequent blood levels.

METHODS

As previously described (28), the Hopkins Lupus Cohort is a prospective study of predictors of flare, atherosclerosis, and health status in SLE. The study cohort includes all patients at the Hopkins Lupus Center who have a clinical diagnosis of SLE and give informed consent to participate in the study. Enrolled subjects are followed quarterly, or more frequently if clinically necessary. The clinical history, laboratory testing, and damage accrual data are recorded at the time of entry into the cohort and are updated at subsequent visits. The

Hopkins Lupus Cohort has been approved by the Johns Hopkins University School of Medicine Institutional Review Board and complies with the Health Insurance Portability and Accountability Act.

Hydroxychloroquine blood levels were measured by liquid chromatography-tandem mass spectrometry as described by Füzéry *et al* (29). The therapeutic range was 500-2000 ng/ml. Our assay has been shown to have acceptable precision over the range 15.7 to 2000 ng/ml. This was chosen as our therapeutic range based on a review of the available literature. Costedoat et al reported a mean level of 1017 +/− 432 ng/ml and in a second work by the same author the mean concentration was 1079 ng/ml with a range of 0-2629 ng/ml. There are inter-individual variations in hydroxychloroquine bioavailability which are considered secondary to pharmakinokinetic and pharmacodynamics factors which are as yet, poorly understood. Levels were taken on the day of clinic assessment and were untimed relative to the last dose of hydroxychloroquine. Given the long half-life of hydroxychloroquine and the previously documented within day variations of less than 8% this was considered appropriate (24). All patients in the cohort were prescribed hydroxychloroquine not to exceed a dose of 6.5 mg per kilogram. The maximum daily dose prescribed is 400 mg. In those who are on hemodialysis 200 mg was prescribed after each dialysis session. In those with renal insufficiency, the dose was 200mg daily.

Starting in January of 2013, blood levels of hydroxychloroquine were measured at each visit for cohort patients who had been prescribed hydroxychloroquine (85% of the cohort). For those in whom a sub-therapeutic level was detected, the patient was counseled to improve compliance. An email was sent on receipt of a low hydroxychloroquine blood level asking that the patient not miss any doses. At their next encounter the low level was highlighted in the chart for discussion.

Lupus disease activity was measured using the Physician Global Assessment (PGA) and the SELENA revision of the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index instrument score (SELENA-SLEDAI)(30) at each visit. The PGA is a well-validated tool which has been used in a large number of rheumatic diseases. It is composed of a visual analogue on a 0-3 scale, with ‘0’ no activity, ‘1’ mild, ‘2’ moderate and ‘3’ most severe. The SELENA-SLEDAI measures lupus disease activity within the last 10 days. It includes 24 clinical and laboratory variables that are weighted by organ system. Disease activity can range from 0–105(30).

Twenty-five hydroxy vitamin D was also measured at each clinic visit with a target level above 40 ng/ml as previously described (31). Patients were prescribed 50,000 international units of Vitamin D (1.25 mg ergocalciferol) weekly if levels were sub-therapeutic.

For statistical analysis the patients were divided according to their blood level. Levels less than 15ng/ml were considered to be consistent with complete non-adherence. Levels of 15-500ng/ml were considered partially adherent (although it is possible that in this group there may be individuals who, due to variations in their metabolism are adherent but achieve lower blood concentrations), between 500 and 2000ng/ml were therapeutic and greater than 2000ng/ml were considered supra-therapeutic. Ideal body was calculated as 45.5 kg + 2.3 kg

per 2.5 cm over 152 cm for women, and 50 kg + 2.3 kg per 2.5 cm over 152 cm for men. We then compared demographic and clinical subgroups with respect to the proportion in each hydroxychloroquine group at their first blood level ("baseline"). Statistical significance of differences was determined based on a Pearson Chi Square Test.

We also compared the hydroxychloroquine groups with respect to mean disease activity levels at baseline and assessed significance using ANOVA. In addition, we performed a within-person analysis by calculating, for each person, their mean activity level during visits when blood levels of hydroxychloroquine were greater than 500 ng/ml and comparing that to their mean activity level during visits when blood levels were less than 500ng/ml. The statistical significance of average differences was assessed using a paired t-test. Finally, to assess the impact of measurement and counseling on HCQ adherence, we compared the proportion of patients with a HCQ level of 500ng/ml or higher based on how many prior assessments of HCQ the patient had.

RESULTS

The demographics of the group at their baseline measurement are outlined in Table 1. The analysis included 686 patients studied over 2,400 visits. One hundred and thirty-eight (20%) individuals had a single blood level taken. The remainder were evaluated on multiple occasions, 357 (52%) had between two and four visits and 191 (28%) were seen on between five and twelve occasions. The patients were for the most part female (n=633, 92%). They were 49% Caucasian, 42% African American and 9% had 'other' ethnicity (mostly composed of Asian and Hispanic patients).

At baseline, 304 patients (44%) had sub-therapeutic levels. Of these, 88 (13%) had levels of hydroxychloroquine in their blood <15 ng/ml indicative of complete non-adherence. Despite appropriate weight based dosing, 16 individuals (2%) were above the therapeutic range.

There were some statistically significant differences seen when demographic groups were compared with respect to the proportion in each hydroxychloroquine group (Table 1). Males were more likely to be in the therapeutic range than females (71% compared with 50%, p=0.050). There were significant differences by age group (p=0.0018 with those under 30 years old and over 60 more likely to be in the therapeutic range). Education and family income did not distinguish any differences in hydroxychloroquine level.

Renal failure (creatinine of over 5mg/ml) was present in 6 individuals (0.8%). Only 1 of these individuals had hydroxychloroquine blood levels in the therapeutic range. In those who had renal impairment, (creatinine 1.4-4.9 mg/ml)) (N=15) 60% were sub-therapeutic. There was one individual with a level of over 2000 in the setting of renal failure. When analyzed by height and ideal body weight across the groups of HCQ concentrations we did not see any significant differences.

Our target for vitamin D is above 40 ng/ml. It is our standard practice that those with levels less than 40 ng/ml are prescribed 50,000 international units of vitamin D per week. The majority of our patients were below target (N=359, 52%). Those with vitamin D levels below our target generally had lower levels of HCQ (p=0.011). There was a correlation

between blood levels of vitamin D and hydroxychloroquine levels (correlation coefficient 0.12, p<0.0022). It is also possible that some of this increase in vitamin D was due to the effect of hydroxychloroquine on the conversion of 25(OH)- to 1,25(OH)2-vitamin D.

There were no differences seen in the distribution of blood levels of hydroxychloroquine by body mass index or disease activity as measured by either SLEDAI or PGA. However the p value for trend for decreasing SLEDAI with increasing blood levels was statistically significant (p=0.04)(Table 2.). Considering those patients who had at least one visit with a hydroxychloroquine blood level of 500 ng/ml or higher, and at least one visit in the sub-therapeutic range, there was not a statistically significant improvement in disease activity when a therapeutic hydroxychloroquine level was achieved (Table 3).

At their first hydroxychloroquine measure, only 56% of the patients had levels above 500 ng/ml consistent with adherence. This proportion increased with each visit, to 80% in those who had 3 visits or more (p <0.0001). See Table 4.

DISCUSSION

This work demonstrates that prior to instituting routine testing, up to 44% of our SLE patients did not take their most important medication as prescribed. This is similar to the reported literature in SLE and in other chronic diseases. In lupus, pharmacy refills have shown 51%(19) are non-adherent to their hydroxychloroquine. In other chronic diseases, studies have consistently shown that 20% to 30% of medication prescriptions are never filled and that approximately 50% of medications for chronic disease are not taken as prescribed(32, 33). In our study, neither income nor education predicted adherence.

In SLE, non-adherence to medication associates with poor outcomes. Julian *et al* (22) reported more outpatient visits and emergency room use in those who had adherence issues. Bruce *et al* (34) reported patient factors were deemed the main reason for renal impairment in 5/17 (29%) individuals with SLE who went on to develop chronic renal insufficiency. In our cohort poor physician global assessment of compliance and patient attendance at routine outpatient appointments were associated with bad outcomes in renal disease (15). Thus, we think that hydroxychloroquine blood monitoring will be cost effective.

Importantly, this work demonstrates that with repeated measurement and patient counseling, adherence can be significantly improved upon. In our study it increased to 80%. Undoubtedly there is inter-individual variation in hydroxychloroquine blood levels. The fact that 80% of patients achieved a level of over 500 ng/ml on repeated testing suggests that a level of over 500 can be considered adherent. In other chronic diseases education and behavioral support have been shown to be effective interventions. This has been shown in renal transplantation (35), hypertension(36-38) and diabetes (39, 40). In the renal transplantation literature medication adherence has been shown to improve with multi-dimensional interventions (41). These conditions are notable in that they all have measurable indications of adherence. In transplant patients, drug levels are routinely monitored. In hypertension the blood pressure can be easily followed and in diabetes decisions are guided by the HBa1C. To date in rheumatology we have not made routine use of any measurable

indication of adherence. Furthermore, the impact of measurement and counseling on patient adherence has not previously been reported in rheumatology. There is a probable Hawthorne effect to be taken into consideration. However, it could be argued that any change in behavior in response to an individual being monitored is the Hawthorne effect. This does not diminish the likely benefits of an intervention.

We do not know whether non-adherence to hydroxychloroquine can be considered an indicator for total medication non-adherence. This is difficult to demonstrate since blood levels of most of our medications are not available. We used vitamin D levels as a surrogate marker for other medications (although hydroxychloroquine can influence Vitamin D metabolism(42, 43)). There was a strong correlation between increasing vitamin D levels and blood hydroxychloroquine levels over time and a statistically significant difference when patients were compared according to their baseline hydroxychloroquine level. This is in contrast to recent work by Schoindre *et al(44)* but there are significant differences in the dosing regimens prescribed (800-1000 iu per day vs. 50,000 iu per week). Our work suggests that improved hydroxychloroquine adherence may be considered a marker for other medication adherence. Although there is a suggestion in the literature that hydroxychloroquine can decrease Vitamin D it is likely that our relatively high dose replacement therapy means that this is not the case in this work.

There was a statistically significant trend towards higher disease activity in those who had low hydroxychloroquine blood levels. This in keeping with the work by Costedoat-Chalumeau *et al* (24) showing that lower levels were associated with higher disease activity. However, within individual analysis over time did not demonstrate improvement in disease activity when therapeutic levels were attained. Similarly, when hydroxychloroquine levels were increased to target, a clinical trial not demonstrate flare reduction with the attainment of therapeutic levels (26). The lack of improvement in disease activity with hydroxychloroquine is disappointing but does not negate the long-term benefits of hydroxychloroquine. The clinical benefit of hydroxychloroquine may lie more in the longterm prevention of flares and thromboses. However, hydroxychloroquine did not reduce severe flares in the Belimumab trials (45). Given the accumulation of hydroxychloroquine in tissues over time, it is possible that tissue levels may grant us better understanding of the relationship between the drug, its mechanisms of action and disease activity. A limitation in this work is the lack of a time on hydroxychloroquine therapy analysis.

All patients in this study were dosed based on weight (and in some cases, renal function) with a maximum dose of 400 mg per day. Despite this, a small proportion (2%) had high levels. It is unclear whether this supra-therapeutic group may represent those who took an extra hydroxychloroquine, whether it may be influenced by their dosing on the day of testing or whether it may relate to decreased clearance. There is current interest in genomic variants that may affect hydroxychloroquine metabolism but we did not have access to these tests. There were no differences in hydroxychloroquine levels when both height and ideal body weight were compared across the different blood concentrations. This suggests that we are correctly dosing patients based on actual rather than ideal body weight (not exceeding a dose of 400 mg per day) and indicated that dosing based on height is unnecessary. In particular

we found that many of our patients with renal insufficiency or failure appeared to be under dosed based on hydroxychloroquine blood levels using our current dosing regimen.

In conclusion, monitoring hydroxychloroquine levels represents an important opportunity to improve medication adherence in patients with SLE. Serial monitoring and dedicated follow up with clinical counseling improved medication adherence. Given the low toxicity (in particular when compared to immunosuppressives and corticosteroids) and improved long-term prognosis with hydroxychloroquine therapy, strategies to maximize adherence are essential. This may have broader applicability to other rheumatological diseases.

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Table 1

Number (%) with Various Levels of Hydroxychloroquine at the first Hydroxychloroquine Assessment by Patient Characteristics

Characteristics	HCQ <15 ng/ml	HCQ 15–500 ng/ml	HCQ 500-2000 ng/ml	HCQ ≥2000 ng/ml	P value
All (n=686)	88 (13%)	216 (31%)	366 (53%)	16 (2%)	
Gender					0.050
Female (n=633)	84 (13%)	206 (33%)	329 (52%)	15 (2%)	
Male (n=53)	4 (8%)	10 (19%)	38 (71%)	1 (2%)	
Ethnicity					0.41
Caucasian (n=333)	37 (11%)	104 (31%)	182 (55%)	10 (3%)	
African-American (n=287)	43 (15%)	86 (30%)	154 (54%)	4 (1%)	
Other (n=66)	8 (12%)	26 (39%)	30 (45%)	2 (3%)	
Age					0.0018
≤30 yrs (n=89)	10 (11%)	18 (20%)	59 (66%)	2 (2%)	
30-44 yrs (n=244)	28 (11%)	98 (40%)	114 (47%)	4 (2%)	
45-59 yrs (n=230)	36 (16%)	75 (33%)	114 (49%)	6 (3%)	
60 + yrs (n=123)	14 (11%)	25 (20%)	80 (65%)	4 (3%)	
Education					0.12
Less than HS (n=51)	5 (10%)	18 (35%)	25 (49%)	3 (6%)	
High school (n=160)	30 (19%)	49 (31%)	78 (49%)	3 (2%)	
Some college (n=465)	52 (11%)	144 (31%)	259 (56%)	10 (2%)	
Family income					0.54
≤$30,000 (n=195)	29 (15%)	59 (30%)	103 (53%)	4 (2%)	
$30,000-$60,000(n=160)	26 (16%)	47 (29%)	84 (53%)	3 (2%)	
Over $60,000 (n=316)	32 (10%)	105 (33%)	170 (54%)	9 (3%)	
BMI					0.26
<20 (n=66)	9 (14%)	20 (30%)	34 (52%)	3 (5%)	
20-24.99 (n=203)	25 (12%)	57 (28%)	114 (56%)	7 (3%)	
25-25.99 (n=185)	30 (16%)	55 (30%)	97 (52%)	3 (2%)	
30+ (n=215)	19 (9%)	79 (37%)	114 (53%)	3 (1%)	
SLEDAI					0.38
0 (n=267)	27 (10%)	83 (31%)	150 (52%)	7 (3%)	
1-3 (n=217)	32 (15%)	71 (33%)	112 (52%)	2 (1%)	
4+ (n=202)	29 (14%)	62 (31%)	104 (51%)	7 (3%)	
PGA					0.37
0 (n=193)	15 (8%)	59 (31%)	114 (59%)	5 (3%)	
>0 to 0.99 (n=301)	42 (14%)	98 (33%)	157 (52%)	4 (1%)	
1.00 to 1.49 (n=80)	14 (18%)	23 (29%)	40 (50%)	3 (4%)	
1.50-1.99 (n=56)	6 (11%)	19 (34%)	29 (52%)	2 (4%)	

Characteristics	HCQ <15 ng/ml	HCQ 15–500 ng/ml	HCQ 500-2000 ng/ml	HCQ ≥2000 ng/ml	P value
2.00+ (n=48)	9 (19%)	16 (33%)	21 (44%)	2 (4%)	
Vitamin D					0.011
< 40 ng/ml (n=359)	55 (15%)	125 (35%)	170 (47%)	9 (3%)	
40+ ng/ml (n=321)	33 (10%)	89 (28%)	192 (60%)	7 (2%)	
Creatinine (mg/ml)					0.029
<1.4 (n=618)	76 (12%)	195 (32%)	334 (54%)	13 (2%)	
1.4-4.9 (n=15)	5 (33%)	4 (27%)	6 (40%)	0 (0%)	
5.0 + (n=6)	1 (17%)	3 (50%)	1 (17%)	1 (17%)	
Height (inches)					0.31
<60 (n=20)	5 (25%)	3 (15%)	11 (55%)	1 (5%)	
60-62.5 (n=221)	22 (10%)	78 (35%)	113 (51%)	8 (4%)	
63-67.9 (n=320)	44 (14%)	97 (30%)	174 (54%)	5 (2%)	
68+ (n=113)	15 (13%)	33 (29%)	63 (56%)	2 (2%)	
Ideal Body Weight					0.82
Less than (n=95)	14 (15%)	28 (29%)	50 (53%)	3 (3%)	
Greater than (n=574)	69 (12%)	183 (32%)	309 (54%)	13 (2%)	

HCQ= hydroxychloroquine, BMI=body mass index, SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, PGA= Physician Global Assessment.

Table 2

Mean (SD) Disease Activity at the First Hydroxychloroquine Assessment, by Hydroxychloroquine Level

	HCQ <15 N=88	HCQ 15-500 N=216	HCQ 500+ N=382	P value
SLEDAI	2.92 (3.62)	2.36 (2.89)	2.20 (2.64)	0.10[1]
PGA	0.75 (0.68)	0.63 (0.63)	0.60 (0.63)	0.14
Vitamin D	37.5 (19.75)	38.40 (16.87)	45.52 (15.56)	0.0021

HCQ= hydroxychloroquine, SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, PGA= Physician Global Assessment.

[1]P=0.040 for trend.

Table 3

Mean SLEDAI and Physician Global Assessment Values for Patients who Experienced at Least One Visit in Compliance (HCQ of 500+ ng/ml) and One Visit Out of Compliance (Hydroxychloroquine below 500 ng/ml)

Measure	Mean (SD) at visits in therapeutic range	Mean (SD) at visits below therapeutic range	Mean (SD) Difference	P-value[1]
SLEDAI (n=246)	2.37 (2.56)	2.51 (3.02)	0.14 (2.35)	0.34
PGA (n=244)	0.65 (0.59)	0.68 (0.64)	0.03 (0.43)	0.30

SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, PGA=Physician Global Assessment.

[1] P-value testing whether difference is significantly different from 0.

Table 4

Proportion of patients in Compliance (blood level of 500+), By Number of Previous Hydroxychloroquine Blood Level Assessments

Number of prior visits with a hydroxychloroquine assessment	Proportion (%) with blood levels of 500 or more*
0	382/686 (56%)
1	379/548 (69%)
2	347/452 (77%)
3 or more	569/714 (80%)

* The p-value for the trend towards higher rates as the visit number increased was <0.0001.