

Low hydroxychloroquine blood levels in patients who have had gastric bypass surgery

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ABSTRACT

Gastric bypass surgery, also called Roux-en-Y gastric bypass (RYGB), can result in the malabsorption of medications, requiring the use of higher than usual doses in order to achieve a therapeutic effect. We describe the results of hydroxychloroquine (HCQ) blood levels in three patients with systemic autoimmune disease taking standard HCQ doses and their associated disease activity levels. This is a retrospective review of all patients who had undergone RYGB and were taking HCQ in a rheumatology community-based practice. Two patients with SLE and one patient with primary Sjogren's syndrome had previously undergone RYGB. All three had subtherapeutic HCQ blood levels and active disease. Increasing their HCQ doses above the recommended 400 mg a day dosing resulted in therapeutic HCQ levels in all three patients and better disease control in two of the three patients. RYGB patients may not absorb HCQ adequately, resulting in subtherapeutic HCQ blood levels and inadequate disease control. Patients who have undergone RYGB and are taking HCQ should have drug levels monitored. RYGB patients may require higher than recommended doses of HCQ in order to achieve better disease control and avoid unneeded additional immunosuppressive agents.

INTRODUCTION

Obesity, commonly defined as having a body mass index (BMI) ≥ 30 kg/m², is a common problem in society. In SLE, some studies show that obesity is associated with higher disease activity and worse outcomes.¹ Bariatric surgery is the most effective treatment for morbid obesity and Roux-en-Y gastric bypass (RYGB), also called gastric bypass surgery, is one of the most common weight loss procedures performed.²

Hydroxychloroquine (HCQ) and other antimalarial medications are the cornerstone immunomodulatory treatment for SLE.³ Most recently, the American Academy of Ophthalmology (AAO) recommended that HCQ should not be dosed above 5.0 mg/kg of actual body weight.⁴ This dosing recommendation was based on the results of a large retrospective study of a Kaiser Permanente Northern California database.⁵ However,

these recommendations have been controversial.⁶ The ability to measure blood HCQ levels in clinical practice has been helpful in identifying patients who are non-adherent to their therapeutic regimens,⁷ often leading to significantly better disease control when confronted with the results.⁸

RYGB surgery can result in the malabsorption of some medications due to changes in the anatomy of the gastrointestinal tract and its effects on gastric and intestinal pH, gastric emptying time, intestinal transit time, surface area for absorption and first pass metabolism.⁹ As bariatric surgery is more commonly performed, the prevalence is increasing among our patients with systemic autoimmune disease, and we need to be cognizant of how it may affect the management of their disease. The currently recommended maximum daily maintenance dose of HCQ is 400 mg/day. However, the oral bioavailability and efficacy of this maximum dose has not been studied in patients who have undergone RYGB surgery.

Here we report two patients with SLE and one patient with primary Sjögren's syndrome who had undergone RYGB surgery, had active disease and low HCQ blood levels on 400 mg daily of HCQ. Considering malabsorption as a potential cause of lower than desired HCQ levels, each patient had their dose raised above the recommended dose, achieving therapeutic levels; two patients had corresponding better disease control as well.

CASES

Case 1

The patient is a 33-year-old, 182-pound (83 kg) Caucasian female (weight range 162–183 pounds; BMI 24.6–27.4 kg/m²) who presented to us in 2017 after presenting with partial complex seizures, posterior cyclitis, inflammatory polyarthritis, photosensitive rash, painful nasal and oral ulcers, malar rash, recurrent pleuritic chest pain, Raynaud's phenomenon,

103°F (39°C) fever, severe fatigue, thrombocytopenia, lymphopenia, non-nephrotic range proteinuria and positive ANA 1:320 homogeneous pattern. Further rheumatological workup disclosed positive chromatin antibody; renal biopsy showed non-specific immunoglobulin M mesangial deposits, and a previous mesenteric lymph node biopsy was consistent with reactive adenitis. Dermatological evaluation agreed with a diagnosis of acute cutaneous lupus lesions by physical examination. Initial treatment consisted of HCQ (two 200 mg tablets taken once a day for a total of 4.8 mg/kg/day), mycophenolate mofetil and intermittent intramuscular corticosteroid injections; she was already on antiepileptic therapy by her neurologist and her 25-hydroxy (OH) vitamin D level was greater than 40 nmol/L while taking ergocalciferol 50 000 IU weekly. Her flares decreased in severity and frequency with this regimen but incompletely. Recurrent steroid-responsive severe headaches with her flares ended up requiring moderate doses of prednisone to provide relief. After several months, subcutaneous belimumab was added 200 mg a week. She continued to have flares with cutaneous, joint and constitutional symptoms. A blood HCQ level was obtained via liquid chromatography coupled with mass spectrometry (testing by Exagen Diagnostics) showing a subtherapeutic level of 593 ng/mL (a therapeutic level is considered ≥ 1000 ng/mL per Exagen). The patient verbally insisted on close to 100% adherence to taking her HCQ, and a verbal conversation between her rheumatologist and pharmacist disclosed regular on-time refills from her pharmacy suggesting excellent adherence. It was noted that she had previously had RYGB surgery in 2009 for the treatment of morbid obesity, so the possibility of malabsorption of HCQ was considered, and her dose was increased to 200 mg three times daily dosing (for a total of 7.4 mg/kg/day). A repeat level 3 months later showed a significantly improved level of 1684 ng/mL while taking 200 mg three times daily. However, she developed central nervous system (CNS) lupus complications at this visit requiring changing her immunosuppressant therapy. Due to having a high HCQ blood level on 200 mg three times daily, her dose was again adjusted to 200 mg twice daily. A repeat HCQ blood level 3 months later was again lower at 520 ng/mL after which we increased her HCQ dose to 500 mg daily (6.7 mg/kg/day) subsequently resulting in a blood level of 1032 ng/mL 3 months later. During all HCQ blood measurements, she had normal renal function with an estimated glomerular filtration rate (eGFR) range of 64–118 mL/min/1.73 m² (normal is >59 mL/min/1.73 m²) and she did not have protein malnutrition from her RYGB (her serum albumin and protein levels were normal).

Case 2

The patient is a 57-year-old, 269-pound (122 kg) Caucasian female (range 220–272 pounds; BMI 37.6–46.1 kg/m²) who was diagnosed with SLE in 1998 manifested by biopsy-proven lupus profundus, lower extremity ulcerations, nonpalpable purpura, photosensitive rash,

inflammatory polyarthritis, hepatosplenomegaly, positive ANA 1:640 nucleolar pattern and a history of antiphospholipid syndrome with three miscarriages, right deep venous thrombosis and positive antiphospholipid antibodies. We started seeing the patient in late 2014 when her treatment was 300 mg/day of HCQ and ergocalciferol 50 000 IU weekly. She had been having intermittent flares of her lupus panniculitis, polyarthritis and severe fatigue. Her labs showed no active serology and her 25-OH vitamin D level was above target at 70.3 nmol/L. She was initially treated with intramuscular corticosteroids and oral methotrexate (MTX) 20 mg a week while also increasing her HCQ to two 200 mg tablets taken together once daily (3.4 mg/kg/day). She had a prompt response with resolution of her polyarthritis and panniculitis. However, over the next few years, she had recurrent, milder flares of her cutaneous, joint and constitutional manifestations; these were treated with intramuscular corticosteroids and increasing doses of MTX (advanced over time to subcutaneous doses). In June 2018, during another flare, her HCQ drug level, while on a dose of 400 mg/day (3.2 mg/kg/day for her body weight at the time), was first measured and was 525 ng/mL. She verbally insisted on close to 100% adherence, and a phone call to her pharmacist confirmed on-time refills of her medications. She had had an RYGB surgery in 2010. The possibility of malabsorption was considered, and her HCQ dose was increased to 200 mg three times daily (4.9 mg/kg/day). A repeat HCQ level 3 months later was much better at 960 ng/mL. She was in remission on that clinical evaluation as well as the subsequent 9 months. During all HCQ blood measurements, she had normal renal function with an eGFR range of 70–104 mL/min/1.73 m², and she did not have signs of protein malnutrition from her RYGB.

Case 3

The patient is a 64-year-old, 259-pound (117 kg) African-American female (range 210–282 pounds; BMI 31.9–44.1 kg/m²) diagnosed with primary Sjögren's syndrome (pSS) by her previous rheumatologist based on a positive ANA, positive rheumatoid factor and keratoconjunctivitis sicca (per her ophthalmologist); she was taking HCQ 400 mg once a day. We began to see the patient in 2010, and because of initially negative autoantibodies, we performed a minor salivary gland biopsy which confirmed the diagnosis with a Chisholm-Mason grade 3. Over the years, she had gradually lost teeth due to xerostomia even while on cevimeline, use of xylitol gum and high-dose fluoride toothpaste. She also had progressive peripheral neuropathy and intermittent bouts of inflammatory arthritis which responded well to intramuscular corticosteroids. In July 2018, during a bout of episcleritis and inflammatory oligoarthritis (shoulder and proximal interphalangeal joint), a HCQ level was checked as a screening test for adherence. Her level was subtherapeutic at 582 ng/mL on 400 mg once a day (3.4 mg/kg/day). She verbally insisted on close to 100% adherence, and her pharmacist confirmed excellent on-time refills as

well. Having had had an RYGB surgery in 2004, the possibility of malabsorption was entertained, and her dose was increased to 200 mg three times daily (5.1 mg/kg/day). A repeat level 3 months later was 829 ng/mL. She had no active arthritis or episcleritis on that occasion nor 9 months later. During all HCQ blood measurements, she had normal renal function with an eGFR range of 60–83 mL/min/1.73 m², and she did not have signs of protein malnutrition from her RYGB.

Discussion

It is recommended that all patients with SLE be treated with an antimalarial medication, most commonly HCQ.³ Out of all the possible side effects, antimalarial-induced toxic maculopathy is the most important potential side effect of HCQ.¹⁰ Fortunately, retinopathy does not occur in most patients who take HCQ. When caught early using the AAO recommended yearly screening tests, mild retinopathy is asymptomatic and does not progress. If HCQ is stopped, the progression of the retinopathy can be halted.^{11 12}

Dosing recommendations for the use of HCQ in the treatment of lupus have fluctuated over time. The Plaquenil brand of HCQ manufacturer's insert recommends prescribing no more than 400 mg/day for lupus, while up to 600 mg/day can be used initially for the treatment of rheumatoid arthritis.¹³ Melles and Marmor evaluated the records of 2361 Kaiser Permanente HCQ long-term users retrospectively.⁵ They identified 163 cases of retinal toxicity using Humphrey central visual field (HVF 10–2) testing and spectral domain optical coherence tomography (SD-OCT) and found that the prevalence of retinal toxicity was least common among patients with an actual body weight dose of less than 5.0 mg/kg. The findings from the Kaiser study led to the AAO recommending that HCQ be dosed at less than 5 mg/kg of actual body weight.⁴

However, this dosing guideline was fundamentally flawed because the Kaiser study was based on the doses the pharmacy dispensed rather than the dose the provider prescribed. A high percentage of patients with chronic illnesses do not pick up some of their prescribed medications at the pharmacy,¹⁴ so the 5 mg/kg dosing that was calculated using the pharmacy-dispensed dose was probably lower than the actual dose the providers prescribed per body weight. We do not know the differences between the pharmacy-dispensed amounts and the provider-prescribed doses, but we know that it is likely that the provider-prescribed dose was somewhat higher. In other words, the actual maximum dose of HCQ to decrease the risk for maculopathy may be 5.5–6.5 mg/kg of actual body weight rather than the reported 5.0 mg/kg guideline recommendation.

Since the AAO used these results to formulate their dosing guidelines, these recommendations are certainly open to question. A further problem with the AAO guidelines is that they only addressed this potential side effect but did not address therapeutic efficacy. It is important

when giving dosing recommendations that both efficacy and potential adverse events be considered together, especially considering how safe and essential HCQ is overall.

Recently, the ability to check blood levels of HCQ has become available in clinical practice. Costedeau-Chalumeau and colleagues showed that patients with SLE with active disease had a significantly lower mean whole-blood HCQ concentration (694±448 ng/mL, similar levels as our three patients) compared with patients with inactive disease (1079±526 ng/mL).¹⁵ Although serum and plasma HCQ levels may also be checked, it has been shown that it is better to check whole-blood levels which are more precise, have higher concentrations, and because of HCQ's preferred binding to albumin, platelets and leucocytes.¹⁶

Measuring HCQ blood levels have also been shown to be an excellent way to check for patient adherence to therapy. Durcan *et al* showed that when their patients with SLE were confronted with low HCQ levels due to non-adherence, not only did adherence significantly improve but lupus disease activity also significantly decreased.⁸ Then, Costedoat-Chalumeau *et al* showed that HCQ blood level measurements identified patients with SLE who were having disease flares related to severe non-adherence. There was poor correlation between actual blood levels and physician assessment of adherence as well as to adherence determinations via patient self-administered questionnaires (the Medication Adherence Self-Reported Inventory). With 68.9% of the flaring patients requiring increased doses of steroids and the poor identification of adherence rates by the physicians (without the use of HCQ levels), the authors recommended the routine use of HCQ level measurements.¹⁷ So far, no HCQ dosing guidelines have taken into account the use of HCQ blood levels.

Other than using actual body weight to determine HCQ dosing, few other parameters have been recommended in helping to determine proper dosing. The absorption and metabolism of HCQ in various patient populations have not thus far been extensively studied. Although HCQ has relatively high absorption from the gastrointestinal tract, we do not know if there are ethnic, genetic or digestive-issue differences in HCQ absorption, metabolism and efficacy. Whole blood concentrations of HCQ vary widely, even after similar dosing in patients.¹⁸ Initial observations from the Plaquenil Lupus Systemic (PLUS) study group showed no association between ethnicity, smoking and antacid or cytochrome P450 enzyme affecting medication interactions with HCQ whole-blood levels.¹⁹ However, high BMI, high estimated creatinine clearance and increased time between the last tablet taken and the measurement of blood levels were associated with lower HCQ concentrations. Patients with chronic kidney disease tended to have higher blood levels.

Currently, the optimal whole-blood level of HCQ to achieve efficacy in the treatment of systemic autoimmune diseases such as SLE is not known. The PLUS study confirmed that lower HCQ whole-blood levels are

associated with higher SLE disease activity. Patients who maintained HCQ levels ≥ 1000 ng/mL tended to have fewer flares over time than those with lower levels.²⁰ However, this persistent level was obtained in a relatively small number of patients.

In our small series of patients (two with SLE and one with pSS), we have identified three patients who had previously had RYGB surgery. All three were taking HCQ at a dose of two 200 mg tablets once a day (total of 400 mg daily), had active inflammatory disease and had HCQ levels similar to the patients with active SLE disease activity in Costedoat-Chalumeau's 2006 study¹⁵; these levels were below our laboratory's therapeutic dose recommendation. Proper adherence to regularly taking their HCQ was confirmed in all three cases by verbal affirmation from the patient and confirmation by each patient's pharmacist stating that the patient was picking up her HCQ prescriptions regularly and on time. Each patient had their dose of HCQ increased to 200 mg three times daily. Three months after each dose increase, each patient had their HCQ level repeated, and all three had significantly improved drug levels. One of the patients with SLE and the one patient with pSS had significantly improved disease control at that time (remission in both); the patient with SLE who had CNS involvement (case 1) did not.

RYGB surgery is one of the most commonly used surgical procedures to treat morbid obesity.³ RYGB is performed by stapling and dividing the proximal stomach creating a small gastric pouch which the surgeon connects to the jejunum (bypassing the body and antrum of the stomach and the duodenum). The effect is that vitamins, nutrients and medications have decreased exposure to gastric acid and no exposure to the absorptive mucosa of the duodenum or the proximal jejunum. It results in a large amount of excess body fat reduction in most patients as well as decreases many of the comorbid conditions. However, chronic malabsorption, especially of micronutrients and fat-soluble vitamins, is an expected consequence requiring lifelong supplementation of these nutrients.

The oral bioavailability of medications can also be affected due to changes in the anatomy of the gastrointestinal tract and its effects on gastric and intestinal pH, gastric emptying time, intestinal transit time, surface area for absorption and first-pass metabolism changes.¹⁷ Some medications have been shown to have lower absorption after RYGB surgery as demonstrated by lower blood levels,²¹ and physicians may need to adjust drug doses due to the possibility of post-RYGB malabsorption.²²

To our knowledge, and after a search of the published medical literature, the oral bioavailability of HCQ has not been studied in patients who have undergone RYGB surgery. RYGB surgery increases gastric pH which can reduce the absorption of medications that are weak bases, such as HCQ.²³ Also, it is a common practice among bariatric surgeons to prescribe proton pump inhibitors (PPI) to prevent gastrojejunal anastomotic ulcerations.²⁴

All three patients were taking a PPI which would increase gastric pH further, which could further reduce HCQ absorption. Although malnutrition is evident in a small percentage of RYGB patients,²⁵ this could be an additional reason for decreased absorption in some RYGB patients.¹⁸

The low levels of HCQ in these three RYGB patients suggest that HCQ may not be adequately absorbed resulting in lower HCQ levels and increasing the potential for inadequate systemic autoimmune disease activity control. Such patients (post-RYGB surgery) may then require the addition of steroids or immunosuppressant medications, increasing the potential risk for side effects. RYGB patients may require adjustments to their HCQ dosing by using higher than recommended doses. The optimal range of HCQ whole-blood levels to achieve the best efficacy balanced with decreased adverse events, such as retinopathy, is unknown. A preliminary study has shown that levels less than 1195 ng/mL are associated with lower retinopathy risk.²⁶ A new paradigm is needed for determining appropriate HCQ blood levels to achieve good efficacy while also avoiding retinal toxicity.

Some caution does need to be used when considering the use of higher than recommended doses of HCQ (>400 mg/day) in patients who have undergone RYGB surgery. A study using 800 mg/day of HCQ (averaging 11.5 mg/kg/day) in patients with graft versus host disease (GVHD) showed that three out of the 12 patients studied developed macular changes suggestive of possible early HCQ retinopathy using SD-OCT, HVF 10–2 and multifocal electroretinography.²⁷ However, these results are probably not applicable to the RYGB population in that they did not have malabsorption, did not have blood levels of HCQ monitored in the study and GVHD itself has been associated with microvascular retinopathy.²⁸

These three patients with systemic autoimmune disease who had undergone RYGB surgery had lower than expected HCQ levels while taking two 200 mg HCQ tablets (400 mg total) at the same time once daily and had active disease activity. All three had significantly improved drug levels after an increase of their HCQ to 200 mg three times daily and two of the three had much better disease control after this dose adjustment. These findings suggest that further study should be done in a larger group of RYGB patients, assessing HCQ drug levels at various dosing regimens while also assessing disease activity and adverse events. Also, two of the three patients had very high BMIs which may have contributed to their low HCQ whole blood levels.¹⁸ The real possibility of malabsorption of HCQ from RYGB surgery deserves to be considered and studied. Up to this time, we may potentially have been undertreating our patients who have undergone RYGB surgery by using subtherapeutic doses of HCQ, resulting in some patients being exposed to additional medications carrying more dangerous side effects. These results need to be assessed and confirmed in larger studies.

Contributors JL is an ophthalmologist who was one of the authors of the American Academy of Ophthalmology guidelines for hydroxychloroquine dosing and retinopathy screening. He assisted in supplying the comments and literature regarding the background for these recommendations and their potential shortcomings and how it pertains to the manuscript. BG is a bariatric surgeon. He assisted in supplying the comments and literature regarding the potential for the malabsorption of drugs in people who have undergone gastric bypass surgery. MP has written several papers regarding the utility of using hydroxychloroquine drug levels in the management of patients with lupus. She contributed comments and articles regarding the proper use of drug levels in these patients and how it could affect proper management of their connective tissue diseases.

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