Adverse Cutaneous Reactions to Hydroxychloroquine Are More Common in Patients With Dermatomyositis Than in Patients With Cutaneous Lupus Erythematosus

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**Background:** Hydroxychloroquine sulfate and other antimalarial drugs have been used successfully as adjunctive therapy for patients with cutaneous lesions of dermatomyositis over the past 20 years. An increased incidence of cutaneous reactions to hydroxychloroquine has been postulated to occur in patients with dermatomyositis.

**Objective:** To determine if adverse cutaneous eruptions due to hydroxychloroquine are more common in patients with dermatomyositis than in those with cutaneous lupus erythematosus.

**Design:** Retrospective, age-, sex-, and race-matched case-control study.

**Setting:** University-affiliated practice.

**Patients:** The study comprised 42 patients with dermatomyositis (39 adults) and 39 age-, sex-, and race-matched adult patients with cutaneous lupus erythematosus.

**Main Outcome Measures:** Presence or absence of documented drug eruption due to hydroxychloroquine exposure.

**Results:** Of 39 patients, 12 (31%) with dermatomyositis developed a cutaneous reaction to hydroxychloroquine. Among age-, sex-, and race-matched patients with cutaneous lupus erythematosus, only 1 developed a cutaneous reaction to hydroxychloroquine. None of the reactions observed in our patients resulted in serious morbidity or mortality. Additionally, 4 patients with dermatomyositis who reacted to hydroxychloroquine were treated with oral chloroquine phosphate, 2 of whom also reacted to chloroquine phosphate.

**Conclusions:** When contemplating antimalarial therapy for dermatomyositis, both the physician and the patient should recognize that non–life-threatening cutaneous reactions may occur in approximately one third of patients and that perhaps one half of those who react to hydroxychloroquine will also react to chloroquine.

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**DERMATOMYOSITIS** (DM) is an idiopathic inflammatory myopathy that has characteristic cutaneous manifestations including the heliotrope rash, Gottron papules, photodistributed erythema or poikiloderma, alteration of the cuticles, and a pruritic scalp dermatitis. Treatment with systemic corticosteroids and immunosuppressive medications usually controls the inflammation of the muscles, but often the skin disease is not fully controlled. Hydroxychloroquine sulfate has been reported to improve the cutaneous manifestations associated with DM.

Cutaneous reactions to antimalarial agents were commonly observed in the treatment of psoriasis and psoriatic arthritis. Similar reactions are unusual in patients with lupus erythematosus (LE). We have observed disease-specific cutaneous reactions to hydroxychloroquine in the treatment of DM. To determine whether an increased frequency of cutaneous reactions to hydroxychloroquine occurs in patients with DM, we reviewed the records of 68 patients with DM and compared them with a group of age-, sex-, and race-matched patients with cutaneous LE.

**PATIENTS AND METHODS**

Approval for research using existing data was received from the Human Studies Committee of the University of Louisville School of Medicine. A list of patients with a diagnosis of DM was computer generated from billing records of the university-affiliated practice. Criteria for the diagnosis of DM were as follows: characteristic skin manifestations as diagnosed by a dermatologist and skin biopsy result consistent with DM, with or without positive serologic findings. Physical examination findings of muscle weakness and/or muscle enzyme analysis, electromyogram and/or muscle biopsy results consistent with myositis supported the diagnosis, but we did not require the demonstration of myositis as a diagnostic criterion. Only patients who had been treated with hydroxychloroquine at some time during the course of their DM were included in the study.
disease were eligible. Patients may have been treated by a referring physician or the therapy may have been initiated upon referral or after other therapies had failed or been demonstrated to be toxic. A follow-up period of at least 2 months was also required for eligibility.

Similarly, a list of patients with a diagnosis of cutaneous LE was generated from billing records for use as controls. Criteria for the diagnosis of cutaneous LE were as follows: characteristic lesions of LE on physical examination by a dermatologist and characteristic findings on skin biopsy. Patient records were selected for further review if the patient had been treated with hydroxychloroquine. Charts of patients with LE were requested from our files and were reviewed to verify diagnosis, ascertain exposure to hydroxychloroquine, and obtain the age, race, and sex of the hydroxychloroquine-treated patients. We then selected 1 such patient to serve as a control for each patient treated for DM. The control patient was matched by age (±5 years), sex, and race. Our protocol called for only 1 matched patient, and although there may have been many other possible matches, these charts were not further reviewed.

Documented cutaneous eruptions to hydroxychloroquine and/or chloroquine phosphate in both groups within 1 month of initiation of therapy were considered positive reactors. We also reviewed the medical records for information about other drug allergies as reported by the patient or observed by a physician and concomitant drug use at the time of the hydroxychloroquine eruption. All patients seen were asked, often repeatedly, about drug allergies. Statistical analysis was performed using the McNemar test on StatXact software (Cytel Software Corp, Cambridge, Mass). A 2-sided $P$ value is reported; $P < .05$ was considered significant.

RESULTS

Eight of the 68 patients qualified as having possible amyopathic DM based on skin findings, biopsy results, and absence of muscle weakness and normal test findings of muscle-derived enzymes. The other 60 patients had evidence of both skin and muscle disease consistent with DM. Of the 68 patients, 42 had been treated with hydroxychloroquine at some time following diagnosis and were therefore eligible for the study. We were unable to match 3 juvenile patients with DM with controls, and thus 39 patients were included in our statistical analysis. Eligible adults with DM ranged in age from 17 to 81 years (mean, 48.8 years). Of the 39 patients, 36 (92%) were women and 37 (95%) were white. The patients with LE were matched for sex and race, and their ages ranged from 20 to 76 years (mean, 47.5 years).

Twelve (31%) of the 39 adult patients with DM developed a cutaneous reaction to hydroxychloroquine (Figure). In comparison, only 1 patient with LE (3%) developed a reaction ($P = .006$). Combined with the 3 juvenile patients with DM, 14 (33%) of the 42 patients overall developed an allergic reaction to hydroxychloroquine. The morphologic features of the cutaneous eruptions were variable. Eleven reactions (79%) were generalized morbilliform eruptions, often intensely pruritic, and all began within 3 weeks of the initiation of therapy. Each resolved on discontinuation of the drug regimen, and many of the patients were treated with tapering courses of oral prednisone. Three of these patients were subsequently started on chloroquine therapy. Two tolerated the drug (although 1 later developed intolerable keratopathy), and 1 developed a morbilliform eruption to chloroquine.

Of the remaining 3 nonmorbilliform eruptions, 1 patient developed an erythroderma within 2 weeks of commencing hydroxychloroquine therapy. She was later given a trial of chloroquine and developed truncal erythema and pruritus. Another patient developed a widespread blistering eruption that was diagnosed as Stevens-Johnson syndrome. She was treated successfully with drug withdrawal and oral prednisone. The final patient developed erythema and edema in an unspecified distribution. None of the cutaneous eruptions were associated with serious morbidity or mortality. The 1 cutaneous reaction in the control patient with LE was morbilliform and resolved on discontinuation of the drug regimen and a short course of oral prednisone.

Dosages of hydroxychloroquine sulfate were either 200 mg daily or 200 mg twice daily in both the patients with DM and LE. At the time of the eruption, 7 patients were receiving no other therapy (6 patients with DM and 1 with LE), 5 were also receiving methotrexate and prednisone therapy, 1 was receiving an antidepressant, and 1 patient’s concomitant drug use was not recorded. Among our 39 adult patients with DM, 8 reported drug allergy to sulfonamides (3 among the 12 patients who had a reaction to hydroxychloroquine and 5 among the group that did not). Among the LE patients, 12 reported sulfonamide allergy, but the patient with the hydroxychloroquine reaction was not allergic to sulfonamides.

Antimalarial agents were first used for lupus in 1894 when Payne treated a case of discoid lupus with quinine. It was not until 1951 that Page reported the benefits of quinacrine for lupus. The use of hydroxychloroquine for the cutaneous manifestations of DM were first described by Woo et al in 1984. They described 7 patients in whom hydroxychloroquine therapy achieved partial or complete clearance of their skin disease and enabled some patients to reduce their dosage of corticosteroids. No adverse events related to hydroxychloroquine were reported in this study. Subsequent case reports and small case series followed, supporting the use of oral hydroxychloroquine for cutaneous lesions of DM.

Bloom et al provided the first report of adverse cutaneous reactions to hydroxychloroquine in patients with DM. They described 2 children in whom the addition of hydroxychloroquine caused exacerbation of existing skin disease and new eruptions. In 1 patient, worsening of Gottron papules and a diffuse erythematous, scaly eruption developed over the posterior neck, thighs, and pretibial skin. The other patient experienced exacerbation of purpura plaques on the face, neck, and arms and a new erythematous, pruritic rash in the axillae. Both patients were using oral corticosteroids concomitantly. Another series of 9 patients with juvenile DM reported good effects with hydroxychloroquine and no adverse reactions when it was used as an adjunct to corticosteroids.

Over the past 20 years of antimalarial therapy for DM at the University of Louisville, it was noted that drug reactions to hydroxychloroquine might occur with an increased frequency. This was in contrast to patients treated for all types of LE, among whom cutaneous reactions were
rare. Our retrospective analysis confirmed that roughly one third of patients with DM developed a reaction and that this is notably different from our experience with its use in patients with cutaneous lesions of LE. We are not able to explain the eruptions on the basis of the patient having an allergy to sulfonamides or receiving concomitant drugs; therefore, it may represent a disease-specific idiosyncratic reaction. There are reports of the successful use of hydroxychloroquine as a corticosteroid-sparing agent; however, the number of patients reported in any one series is small, which might account for the previously small numbers of reactions that have been reported. Fortunately, in none of these cases were the drug eruptions life threatening, most (79%) were generalized morbilliform eruptions. In addition, 2 of 4 patients given a trial of chloroquine following an adverse reaction to hydroxychloroquine developed a cutaneous reaction.

Our results indicate that treatment of adult DM with hydroxychloroquine is associated with adverse cutaneous events in approximately one third of cases. Regarding juvenile patients with DM, our series and other series indicate that their risk of cutaneous reactions is also elevated. Patients with cutaneous LE do not experience an increased frequency of such reactions. In our experience, such information should be discussed with patients with DM prior to commencing therapy. Alternative therapies do exist; therefore, the decision to use hydroxychloroquine must be made on a case-by-case basis. Alternative therapies, such as methotrexate, chlorambucil, mycophenolate mofetil, and thalidomide, may have inherent risks and adverse effects that justify the increased risk of cutaneous reactions to antimalarial agents in selected patients. Although we did not assess the clinical response to hydroxychloroquine in patients who tolerated the drug, our experience continues to support the beneficial effects in many patients with DM with refractory cutaneous disease.

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REFERENCES


In this article, Pelle and Callen report a strong association between the development of rash in patients with dermatomyositis who take hydroxychloroquine compared with similarly exposed patients with lupus. The criteria to appraise the validity of such a study about harm include similarity of the comparison groups with respect to important determinants of outcome; similar measurement of outcome and exposure in the groups; sufficient length of follow-up; and correct temporal relationship between exposure and adverse events (Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V, for the Evidence-Based Medicine Working Group. Users’ guides to the medical literature, IV: how to use an article about harm. JAMA. 1994;271:1613-1619). This study meets these quality criteria quite well. The strength of association in case-control studies is typically expressed as the odds ratio and its 95% confidence interval (12 [1.8 to 525] in this study). Pelle and Callen provide reasonable advice as to how the data should be applied to patient management. The study represents level 3B evidence (http://163.1.96.10/docs/levels.html) and should be confirmed by others.

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