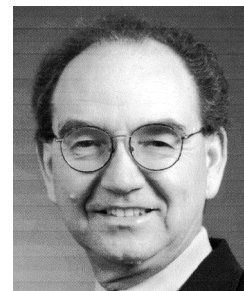


Desensitization to Hydroxychloroquine: Alternative Interpretations



Considering the increasingly important role of the aminoquinoline antimalarials (AA) in the management of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), Mates and coworkers are to be congratulated for addressing an important clinical issue in the management of antimalarial cutaneous adverse reactions¹. However, their report raises several important issues not commented upon by these investigators. We wish to offer an alternative interpretation to the results of their proposed desensitization protocol and provide a broader perspective on clinical issues related to AA cutaneous adverse drug reactions.

A pruritic maculopapular eruption that was presumably symmetrically distributed on the trunk and extremities occurring 1–2 weeks after starting hydroxychloroquine (presumably hydroxychloroquine sulfate; HCQ) was reported in all 4 cases described by Mates, *et al.* Although skin biopsy results were not presented, this pattern of cutaneous hypersensitivity would appear to be best classified as a simple drug-induced exanthem (synonymous with exanthematous drug rash/eruption, maculopapular drug rash/eruption, morbilliform drug rash/eruption, rubelliform drug rash/eruption, scarlatiniform drug rash/eruption)².

The following list presents a more complete menu of the clinicopathological patterns of cutaneous adverse drug reactions that have been associated with AA³.

Patterns of cutaneous hypersensitivity reactions seen with aminoquinoline antimalarials³.

- Acute generalized exanthematous pustulosis
- Angioedema
- Bullous eruptions
- Erythema annulare centrifugum
- Erythema multiforme
- Erythroderma
- Exanthems
- Exfoliative dermatitis
- Fixed drug eruption
- Lichenoid eruption*
- Photosensitivity
- Polymorphous light eruption

* This pattern of cutaneous adverse drug reaction can be a harbinger of severe AA-induced bone marrow toxicity⁴.

- Psoriasis (exacerbation)
- Pustular eruption
- Rash [sic]
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Urticaria
- Vasculitis

An exanthem is the most commonly noted cutaneous adverse reaction pattern to all drugs, ranging between 51% and 95% in various series^{5,6}; it is also the most common cutaneous adverse reaction to AA⁷.

Other than the suggestion that hydroxychloroquine-induced exanthems might be more common in dermatomyositis than in other disease settings⁷, drug-induced exanthems produced by AA are not significantly different in clinical features or prognosis from drug-induced exanthems produced by a host of other more commonly employed agents including antibiotics, anticonvulsants, antiinflammatories, and allopurinol. In addition, a number of viral infections can produce cutaneous exanthems that closely simulate or are identical to drug-induced exanthems. It has been speculated that concurrent infections might actually represent a priming factor for the development of drug-induced exanthems. The frequency of amino-penicillin (ampicillin, amoxicillin) induced exanthematous eruptions in infectious mononucleosis approaches 100%⁸.

It is typical for drug-induced exanthems to resolve spontaneously even if the offending drug is not discontinued. Thus if necessary, one can “treat through” drug-induced exanthems, including AA-induced exanthems⁸. However, this should be done with vigilance, as extension of the cutaneous injury pattern to a potentially more serious one is possible, such as exfoliative erythroderma, delayed drug hypersensitivity reaction (synonymous with drug rash with eosinophilia and systemic symptoms, drug-induced delayed multiorgan hypersensitivity syndrome), Stevens-Johnson syndrome, or toxic epidermal necrolysis. However, such extension appears to be quite rare. Treating through other patterns of AA cutaneous adverse drug reactions (Table 1) such as lichenoid eruptions, vasculitis, and exfoliative dermatitis has generally been felt to carry too much risk to be recommended.

Drug-induced exanthems are also characterized by their

frequent failure to reappear following oral challenge with the offending drug. In a recent study, 784 patients having prior cutaneous adverse drug reactions of various types (predominately drug-induced exanthem, fixed drug eruption, and urticaria) underwent 1001 oral challenges with the offending agent over a 25 year period. The prior cutaneous adverse drug reaction in 51% of these 784 patients was thought to be a drug-induced exanthem. Skin test-positive patients and patients having a history of serious cutaneous adverse drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe angioedema were not challenged. Only 13% of the patients challenged developed a positive challenge reaction⁵. Seventy-one percent of the positive challenge reactions were drug-induced exanthems.

It is possible, therefore, that delivery of increasing doses of HCQ suspension over time in the desensitization protocol described by Mates, *et al* was a null event rather than one that induced immunological tolerance to HCQ. It would seem premature for the authors to speculate about tolerance-inducing capabilities of this desensitization regimen based on the data presented.

The histopathology of drug-induced exanthems is marked by the presence of skin-homing CLA+, CD4+ T cells bearing activation surface markers [interleukin 2 (IL-2) receptor, HLA-DR, lymphocyte function-associated antigen-1, L-selectin) that are focused in a perivascular distribution (primary data summarized in Lerch, *et al*², Yawalkar⁹). The associated dermal microvascular endothelial cells display activation markers including E-selectin and P-selectin. Eosinophils are also frequently seen in association with activated dermal T cells thought to be the result of eosinophil chemotaxis from local production of IL-5, eotaxin, and RANTES. In addition, activated CD4+ T cells and CD8+ T cells expressing cytotoxicity markers (perforin, granzyme B) are seen at the dermal-epidermal junction in an interface dermatitis pattern that includes vacuolar degeneration of activated keratinocytes in the epidermal basal layer⁹. It has been suggested that activated keratinocytes expressing HLA-DR and various adhesion molecules might be capable of presenting drug-related antigens to previously sensitized infiltrating T cells.

These observations are consistent with the hypothesis that drug-induced exanthems result from cytotoxic cellular injury within the upper dermis and epidermal keratinocyte basal layer resulting from a conventional T cell-mediated delayed hypersensitivity mechanism involving immunologic memory. This is supported by the observation that 70% of patients with drug-induced exanthems display positive drug patch tests or lymphocyte transformation tests². However, the observations that 30% of such patients do not display positive drug patch tests or lymphocyte transformation tests and the majority of patients with drug-induced exanthems do not display a positive oral challenge test suggest that other danger signals might be necessary for the complete

clinical expression of a drug-induced exanthem. As previously discussed, concurrent viral infections that activate the cutaneous innate immune response might represent such a danger signal.

There are several other management options that can be considered when faced with patients who experience AA cutaneous adverse drug reactions, including oral challenge with alternative AA structures. Few published data exist concerning oral challenge with chloroquine in patients who have demonstrated a HCQ sulfate-associated drug-induced exanthem. Pelle and Callen reported that only one of 3 patients with dermatomyositis who had exhibited HCQ sulfate-associated exanthems re-expressed the exanthem after oral challenge with chloroquine phosphate⁷. It has been the personal experience of members of the North American Rheumatic Skin Disease Study Group Organizing Committee that chloroquine phosphate can be administered to patients who have experienced prior HCQ sulfate-associated exanthems with a low risk of re-expression of the exanthem or appearance of other clinical forms of cutaneous hypersensitivity. This might be explained in several ways: (1) the above noted tendency of some cutaneous adverse drug reactions such as drug-induced exanthems to fail to reappear upon challenge; (2) lack of immunological crossreactivity between the 2 closely related base structures of HCQ and chloroquine; (3) antigenic differences relating to the different salt moieties of HCQ sulfate and chloroquine phosphate; and/or (4) differing excipient profiles of tablets of the same drug from different manufacturers.

Multiple excipients have been implicated as the cause of cutaneous adverse drug reaction¹⁰. Tablets from different manufacturers containing the same AA base molecule and salt can differ in the excipients they contain¹⁰. Also, tablets containing different salt forms of the same AA base can have different excipient profiles¹⁰. There are currently at least 2 tablet forms of HCQ sulfate on the US market, one branded product [Plaquenil (Sanofi-Aventis)] and one generic product. Mates, *et al* did not indicate whether the specific tablet form of HCQ used in their oral desensitization protocol was identical (i.e., from the same manufacturer and lot number) to the one implicated in the original cutaneous adverse drug reaction experienced by their 4 patients. Thus, we cannot be certain that the commercial form of HCQ tablets that were used to prepare the desensitization solutions was the same as that which produced the original cutaneous adverse drug reactions. Without this knowledge, it is possible that the original HCQ associated exanthems were produced by one or more excipients that were not present in the desensitization solutions.

We are fortunate that the work of Mates, *et al* has brought into focus several important clinical issues relating to AA adverse cutaneous reactions. However, their work also illustrates the need for more systematic study in this area.

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Comment

Desensitization to Hydroxychloroquine

Drs. Mates and Nesher reply

We appreciate Dr. Sontheimer's comprehensive discussion on hydroxychloroquine (HCQ) hypersensitivity reaction¹, stimulated by our recent report describing a protocol of desensitization to HCQ². We would like to clarify and comment on several issues raised by this editorial.

The manufacturer of Plaquenil (hydroxychloroquine sulfate) given to the patients was Sanofi-Synthelabo (Paris, France). The same product was used in the desensitization procedure.

HCQ rechallenge was attempted in one of our 4 patients prior to desensitization, and resulted in very rapid reoccurrence of diffuse rash, associated with shortness of breath. As a consequence, we did not try to rechallenge the other 3 patients. Such a rechallenge could indeed have been uneventful in some of the other patients, but given our experience with one patient and the severity of the rash in the others, we elected not to attempt any more rechallenges.

Dr. Sontheimer suggests another management option to consider when faced with patients who experience HCQ cutaneous adverse reaction — a trial of chloroquine. Although challenge with chloroquine may not result in reexpression of the rash, one should bear in mind the increased retinal toxicity of chloroquine^{3,4}. Therefore, attempting desensitization to HCQ seems preferable.

We appreciate the attention our report has created, and hope it would enable more patients to safely continue treatment with this medication.

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