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MINI-REVIEW

Hydroquinone Therapy for Post-inflammatory Hyperpigmentation Secondary to Acne: Not Just Prescribable by Dermatologists

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Post-inflammatory hyperpigmentation after acne can be as troublesome as the acne itself. Hydroquinone, a tyrosinase inhibitor, in a 4% cream can be used safely twice daily for up to 6 months to treat post-inflammatory hyperpigmentation. The efficacy of this treatment can be enhanced by using a retinoid nightly and a mid-potent steroid, which is applied twice daily for 2 weeks, then at weekends only. Combination creams help with compliance, but often lack the strongest individual ingredients. Because steroids should not be applied to the face for prolonged periods, care should be taken when a hydroquinone cream containing a steroid is chosen. If post-inflammatory hyperpigmentation consists of a few lesions, spot therapy is useful. If post-inflammatory hyperpigmentation consists of many lesions, field therapy is favored. Safety concerns with hydroquinone consist only of occasional irritation, which can be suppressed with topical steroid or a short drug holiday. Physicians should feel comfortable to use hydroquinone without consulting a dermatologist. ***Key words: hydroquinone; acne; adolescent; post-inflammatory hyperpigmentation.***

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Nearly 50 million Americans have acne vulgaris each year (1), making it one of the most commonly encountered conditions in primary-care and dermatology practices nationwide. Post-inflammatory hyperpigmentation (PIH) often develops secondary to either the acne itself or to damaged skin caused by overly aggressive treatment. Clinically, PIH presents as localized or diffuse brown macules at sites of former acne papules and pustules (Fig. 1). The skin discoloration, which is due to excess melanin, may persist for several months or even years. Many patients find the persistent PIH more psychologically disturbing than their original acne lesions (2). It is important for physicians to recognize the negative impact that acne and PIH can have on a patient's emotional health (causing anxiety and depression), as well as on his or her social interactions, self-esteem, self-confidence, and even employment opportunities (3).

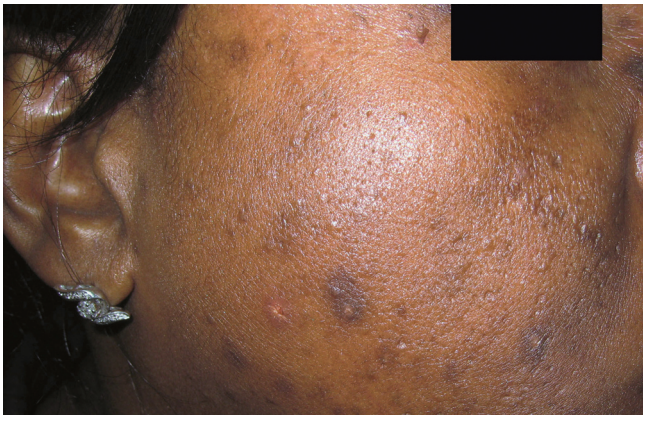

Fig. 1. Post-inflammatory hyperpigmentation due to acne in a dark skin-type.

Hydroquinone, a skin-bleaching cream, is the gold-standard for treating PIH and other disorders of hyperpigmentation, such as melasma and solar lentigines (4). It is indicated for patients age 13 years and up. Hydroquinone has been produced in various over-the-counter (OTC) and prescription formulations in the USA for over 55 years, with only exceedingly rare adverse reactions reported (5). OTC hydroquinone 2% preparations are typically less effective than the prescription 4% preparations. Adolescents are among those affected by acne, and a significant subset of these patients will experience related PIH. However, the majority of hydroquinone prescriptions written in the USA are done so by dermatologists. Indeed, from November 2009 to November 2010, a total of 470,964 hydroquinone prescriptions were written in the USA (excluding in-office dispensing), out of which 252,066 were written by dermatologists, 72,346 by primary care physicians, and another 146,552 by other specialty physicians (6). This paper aims to make the physician more comfortable with hydroquinone therapy by delineating how to use hydroquinone for PIH secondary to acne, as well as the drug's mechanism of action and safety profile.

PATHOPHYSIOLOGY OF POST-INFLAMMATORY HYPERPIGMENTATION

In normal skin, melanocytes (specialized dendritic cells located at the dermal–epidermal junction) convert

tyrosine into melanin via the enzyme tyrosinase. This process occurs within specialized intracellular vesicles called melanosomes, which are then transferred to keratinocytes and sent to the epidermal surface. The quantity, melanin content, and distribution of these melanosomes determine the various hues of human skin color (7).

Hyperpigmentation disorders usually result from an increase in melanin production, and less commonly, from an increase in the number of active melanocytes (7). The most important risk factor in the development of all hypermelanotic conditions is ultraviolet (UV) irradiation from sun exposure, although in acne, inflammation plays an equal if not more important role. Even minimal sunlight sustains melanocytic activity. Because exposure to UVA and UVB light leads to melanocytic growth and increased transfer of melanosomes to keratinocytes, broad-spectrum sun-blocks are an essential adjunct to any treatment regimen for hyperpigmentation (8).

PIH frequently develops secondary to cutaneous inflammation or injury (7). Acne vulgaris is one of the most common inflammatory skin disorders that results in hypermelanosis (2). All age groups are equally affected, and there is no difference between genders; however, PIH is more likely to develop in patients with darker skin types (7). The time of onset of hyperpigmentation relative to the inciting inflammation has never been studied rigorously, but it typically evolves over a few days. The hyperpigmentation frequently becomes apparent only after the erythema has resolved.

The skin discoloration of PIH, which is caused by excess melanin within the epidermis and/or dermis, ranges in color from either tan to dark brown (epidermal melanin) or gray-blue to gray-brown (dermal melanin). Epidermal hyperpigmentation results from increased melanin production and/or melanosome transfer to keratinocytes. This melanin will be shed with the monthly turnover of the epidermis. In contrast, dermal hyperpigmentation develops when melanin crosses the damaged basement membrane, where it is phagocytosed and retained by dermal macrophages, sometimes permanently (7).

MECHANISM OF HYDROQUINONE

Hydroquinone, or 1,4-dihydroxybenzene, is a phenolic bleaching compound that is the gold-standard therapy for PIH. The mechanisms of action of this drug include: (*i*) reversible inhibition of tyrosinase (the main enzyme involved in the conversion of tyrosine to melanin); and (*ii*) selective damage to melansomes and melanocytes (7). Therefore, the mechanism of action of topical hydroquinone is through prevention of new melanin production. As skin cells mature, the melanin-containing keratinocytes within the epidermis are shed and new keratinocytes are formed with less pigmented melanosomes (7). As depicted in Fig. 2, the epidermis effectively lightens over time. Hydroquinone is relatively ineffective against dermal hyperpigmentation because it cannot penetrate the dermal–epidermal junction and dermal melanin that is already present has less means of egress.

Because the amount of time that elapses between the initial inflammation and development of hyperpigmentation is unknown, when to begin hydroquinone therapy remains subjective. Theoretically, one would prefer initiating therapy prior to the onset of PIH (i.e., at the onset of an inflammatory acne lesion); however, that would require adding a hydroquinone cream to an often topical-intensive acne regimen. Compliance, and possibly drug incompatibility (in the case of benzoyl peroxide and hydroquinone), are limiting factors. More often, hydroquinone therapy is initiated once the acne is under control or resolved.

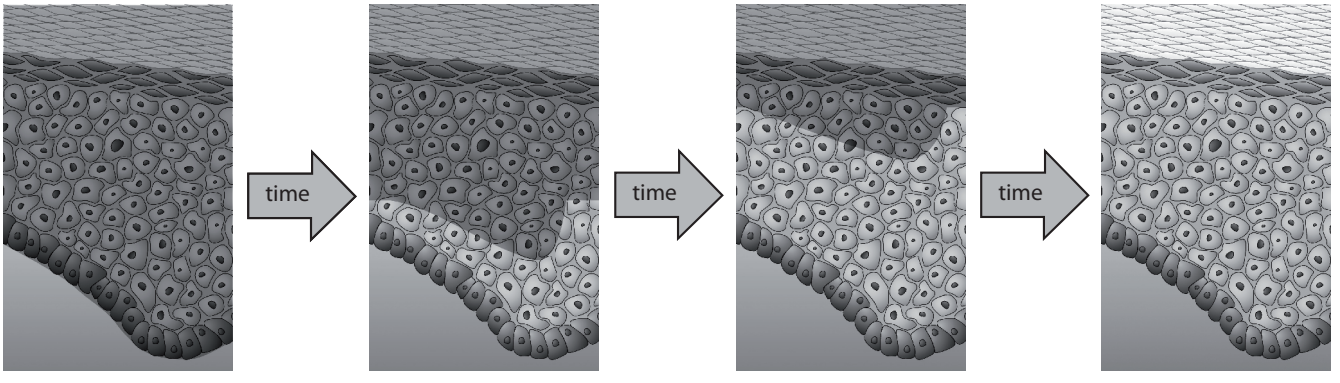

Fig. 2. Schematic depicting the progression of skin lightening that occurs as epidermal melanin is shed while preventing new epidermal melanin formation. In dyschromia, excess melanin is found in skin cells throughout the epidermis. As skin cells mature, cells containing melanin are shed. When new melanin production is inhibited, the rate of new melanin production is less than the rate melanin is shed. Thus, the skin lightens. The process occurs over 1–6 months, depending on the physician's ability to quell the inciting trigger for local excess melanin formation (i.e., in the case of acne, the ability successfully to treat the acne and/or protect the pigmented area from ultraviolet light).

HYDROQUINONE TREATMENT REGIMENS

In 1975, a new formula was introduced by Kligman & Willis (9) for the effective treatment of hyperpigmentation that consisted of hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%. Known today as "Kligman's formula", this combination was found to be more therapeutically effective in treating PIH, melasma, and ephelides than any of the three components independently. In fact, Kligman reported that his formulation achieved complete depigmentation in normal skin of black patients when it was applied daily for 5–7 months (9).

Given the observations of Kligman & Willis, maximal PIH therapy of the face should include hydroquinone 4% or 5% (4% is the strongest available prescription concentration available without compounding in the USA), a mid-potent steroid, a topical retinoid, and sunscreens. The hydroquinone should be applied twice daily for 2–6 months. If no results are seen after 2 months, it should be discontinued. Therapy beyond 6 months is not expected to yield additional improvement when positive results are seen. Because long-term steroid side-effects include cosmetically unappealing cutaneous atrophy, marked by striae distensae, telangiectases, and steroid acne, it should be used twice daily for 2 weeks then once to twice weekly thereafter. Signs of skin thinning or excessive skin lightening are an indication to stop using the steroid. These side-effects, and therefore use limitations, are expected of any class of steroid, whether low or medium potency. As such, a mid-potent steroid allows for maximal efficacy. A topical retinoid should be chosen on the basis of balancing skin irritation vs. efficacy. Gentle retinoids include retinol 0.3% applied twice daily, which, in combination with hydroquinone 4%, has been show to have comparable skin lightening effects to tretinoin 0.05% applied nightly (10). Stronger retinoids include tazarotene 0.1% cream (the gel formulation tends to be more irritating). Because tazarotene can be irritating if left on all night, one method for applying it is to leave it on for 2 min and then wash off, increasing the application time by 2 min every 4 days. Once 7–10 min is reached, it can be left on all night (11). Finally, sunscreen with an SPF of ≥ 15 should be applied in the morning and every 2 h thereafter if going in the sun.

Because 4 different agents are needed for the optimal treatment of PIH, combination creams become an important adjunct to therapy. The ideal combination would allow for twice daily dosing of hydroquinone and sunscreen with SPF 15 or greater (since patients may not comply with additional applications (12)), with our without a gentle retinoid that could be used twice daily without being overly irritating. Independent control over both the steroid and the retinoid is favored, allowing for limited use of a mid-potent steroid and titration of retinoid potency.

While a triple combination cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% is available, the presence of the steroid forces its long-term use, raising concern for telangiectases and steroid atrophy. As stated above, twice daily application of hydroquinone is favored; however, the irritation of tretinoin 0.05% limits this combination to once daily use. It also does not contain a sunscreen (13).

Because hydroquinone lightens the skin and because PIH due to acne results in discrete macules of hyperpigmentation, the question arises whether to apply the treatment as spot therapy or as field therapy. Spot therapy spares lightening of otherwise normal skin, but can, over time, leave a halo of hypopigmentation that normalizes over a period of weeks. In spite of this occasional occurrence, spot therapy is appropriate for patients with only a few macules of PIH. Those with many or clustered macules of PIH should simply apply the creams to the entire affected field. Skin lightening occurs gradually over time, such that the patient can stop applying the medications once desired lightening is achieved, the thereby maintaining excellent control over the degree of lightening.

The objective of therapy is to make the hyperpigmented macule achieve the same tone as the skin at baseline. With pure epidermal pigmentation, after successful treatment, the tone of the surrounding normal skin and the hyperpigmented macule should become identical, even if both are lighter than the baseline skin tone. Results are usually noticeable after 8–12 weeks of treatment (2). With resolution of the inciting inflammatory stimulus, skin should re-pigment evenly to the baseline skin tone in approximately 1–2 months after discontinuation of therapy. It is important for both patients and physicians to have realistic expectations for hydroquinone therapy. Although perfect skin tone will never be attained, due to hydroquinone's inability to treat dermal hypermelanosis, a softening of pigment contrasts can be achieved that results in patient satisfaction and/or easier concealment with facial cosmetic products.

SAFETY OF HYDROQUINONE

The US Food and Drug Administration (FDA) recently presented several key safety concerns regarding hydroquinone. Their primary issue was in response to reports that oral hydroquinone causes cancer in rodents fed copious amounts of the drug (14). However, oral consumption does not reflect the miniscule doses related to topical application, and no cases of human carcinogenicity have ever been reported in over 30 years of use (4). The FDA was also concerned about South African reports of exogenous ochronosis secondary to hydroquinone in black people (14). The majority of these patients used high concentrations of hydroquinone-containing products on large areas of skin, multiple times a day, with exag-

gerated overuse, for years. Often, the products contained confounding agents, such as resorcinol, that also cause exogenous ochronosis. Hydroquinone therapy in the USA differs from, and is safer than, that in Africa with respect to government regulation, formulation, concentration, amount used, and application frequency and duration (4, 15). Therefore, it is not surprising that there have been less than 25 reported cases of exogenous ochronosis in the USA in more than 50 years. Considering that 10–15 million tubes of skin-lightening products containing hydroquinone are sold per year in the USA the number of cases of exogenous ochronosis is extremely low and virtually absent in the context of prudent, supervised use (15). Mild erythema can be expected due to irritancy of hydroquinone, but this is rare and concentration-dependent, frequently occurring when concentrations greater than 4% are used (9). Such irritation can be suppressed with a topical steroid or a short drug holiday. Finally, most hydroquinone preparations contain sodium metabisulfite, a preservative that very rarely causes hives, itching, wheezing, anaphylaxis, and severe asthma attacks in susceptible persons.

CONCLUSION

In conclusion, the gold standard therapy for hyperpigmentation disorders, including PIH secondary to acne vulgaris, is hydroquinone. The drug works by inhibiting new epidermal melanin production. Hydroquinone has been proven to be safe and effective for treating hyperpigmentation in patients aged 13 years and older when used as directed. PIH associated with acne is an extremely common condition that may lead to long-term psychosocial problems for patients, especially adolescents, where cosmesis and social acceptance are major issues. Therefore, it is incumbent upon the physician to become comfortable with hydroquinone and make this therapy available to their patients who have PIH.

The authors declare no conflict of interest.

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