Skin Care in Patients With Pigmentary Disorders

Zoe Diana Draelos, MD

Dermatologists frequently are challenged by patients who request improvement of facial pigmentation. It is unfortunate that skin lightening is a slow, long-term process that does not produce results in the time frame desired by most patients. The most popular skin-lightening preparation used in the prescription realm is hydroquinone (HQ), but recently it has been mired in regulatory controversy. Hydroquinone is an unstable compound that has withstood the test of time but actually may be toxic to melanocytes, particularly if used in an oxidized form. It is not desirable to injure melanocytes, but suppression of pigment production may result in improved skin appearance. Nevertheless, HQ can cause skin irritation and must be used in concert with complementary skin care products. This article focuses on skin care techniques for patients with pigmentary disorders.

Melanin Suppression and the Skin Barrier

Topical products used to improve pigmentation are applied to the stratum corneum, which is not the site of pigment production. Some skin-lightening products, such as those containing glycolic or salicylic acid, are intended to temporarily improve pigmentation by inducing exfoliation of the pigmented corneocytes, which also is the mechanism for the skin-lightening effect of microdermabrasion. These techniques are not sufficient for skin-lightening alone because they do not affect melanization.

All other topical skin-lightening formulations contain active ingredients that suppress melanin production by inhibiting tyrosinase, decreasing melanin transfer to melanosomes, or competing for raw materials required for melanin synthesis, which means that topical skin-lightening agents must penetrate the stratum corneum to reach the base of the viable epidermis where the melanocytes reside. This process is rather challenging because the stratum corneum is best at keeping chemicals out of the skin. Successful skin-lightening preparations must contain penetration enhancers that damage the stratum corneum, such as propylene glycol. Penetration enhancement is the rationale behind the use of tretinoin in combination with HQ, either by applying the 2 products separately or using combination formulations.

Unfortunately, most skin-lightening preparations damage the skin's barrier, causing sensitive skin, which results in stinging and burning that may prohibit further use of the treatment or instigate an intolerance to other skin care products. Therefore, skin care products selected for use should maximize barrier function.

Maximizing Barrier Function

Cleansing is the most damaging activity for the skin barrier. Many patients with facial dyspigmentation think they can scrub the pigment off their skin, as they would with dirt. Dermatologists know it cannot be done and should discourage the use of aggressive particulate scrubs with fruit pigments, nut fragments, or polyethylene scrubbing beads. Patients also should avoid home dermabrasion machines, aggressive mechanized facial brushes, and needling devices. A popular trend in Asia and Europe is to apply skin-lightening products and then use a roller that contains small, tapered, stainless steel needles. The roller is pushed into the skin, creating small columnar wounds through which skin-lightening ingredients are traumatically pushed into the viable epidermis. Many patients prefer this treatment because the temporary edema created by the puncture wounds minimizes fine lines and also appeals to the "no pain, no gain" philosophy of beauty. This technique, known as needling, is used as a means of mechanical penetration enhancement for many topical agents.

Photoprotection

Ideally, patients should apply their prescription product in the morning as well as a sunscreen-containing moisturizer. The moisturizer will decrease transepidermal water

From the Department of Dermatology, Duke University School of Medicine, Durham, North Carolina.

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Correspondence: Zoe Diana Draelos, MD, 2444 N Main St, High Point, NC 27262 (zdraelos@northstate.net).

loss and minimize barrier damage while also providing photoprotection. Patients should select a sunscreen-containing moisturizer with a minimum sun protection factor (SPF) of 30 because lower SPF products may not provide adequate UVA photoprotection, which is the action spectra for facial pigmentation. Ideally, the sunscreen-containing moisturizer should combine both organic and inorganic filters to absorb and reflect UV radiation. Further photoprotection can be achieved by applying a facial foundation followed by a facial powder.

Cosmetics

Colored cosmetics can be a source of photoprotection in patients with dyspigmentation. Facial foundation contains iron oxide, zinc oxide, and kaolin, all providing physical, broad-spectrum photoprotection. Many facial foundations also contain organic sunscreens, using octyl methoxycinnamate and oxybenzone to provide an SPF rating. It is important to remind patients, however, that the SPF of their sunscreen-containing moisturizer and facial foundation is not additive; rather, multiple applications of sunscreen-containing products provides a thicker, more even film, and the amount of photoprotection provided is more likely to approach the bottle rating.

Facial powders applied on top of facial foundation can provide even more photoprotection by keeping the foundation in place while also coating the skin with an additional layer of kaolin, talc, and iron oxide. Facial powders also absorb sweat and sebum that can destroy the film created by the facial foundation and literally float the photoprotective elements right off the face. They can be dusted with a loose brush over the foundation that has been applied on top of the sunscreen-containing moisturizer.

Patients with dyspigmentation require as much photoprotection as possible. Never forget to recommend a hat, scarf, umbrella, and big sunglasses, as well as cosmetics.

Prescription Skin-Lightening Agents

The gold standard for hyperpigmentation therapy in the United States continues to be HQ.[1] Hydroquinone use actually is quite controversial, with HQ products having been removed from the over-the-counter (OTC) markets in Europe and Asia. Concern initially arose because oral HQ was reported to cause cancer in mice that were fed large amounts of the substance. Although oral consumption probably is not related to topical application, HQ remains controversial. A phenolic compound chemically known as 1,4-dihydroxybenzene, HQ functions by inhibiting the enzymatic oxidation of tyrosine and phenol oxidases. It covalently binds to histidine or interacts with copper at the active site of tyrosinase. It also inhibits RNA and DNA synthesis and may alter melanosome formation, thus selectively damaging melanocytes. These activities suppress the melanocyte metabolic processes and induce a gradual decrease in melanin pigment production.[1]

Hydroquinone is available in both the OTC and prescription US markets. The maximum concentration in OTC formulations is 2% and most prescription formulations are 4%. It is possible to compound HQ creams with a concentration as high as 8%, but the formulations are unstable with rapid oxidation represented by browning of the product. The US Food and Drug Administration issued a guidance frowning on the extemporaneous compounding of prescription agents because the compounded products have not been approved and may not be stable as formulated.[2] It is a gray area of the regulatory law, but dermatologists should realize that they might find themselves on the short end of the stick if problems arise from using compounded materials.

Hydroquinone is particularly difficult to formulate because it is highly unstable. Most patients notice that the small amount of product left around the opening of the tube will turn brown, which happens when the HQ is oxidized after coming into contact with oxygen outside the tube. For this reason, HQ must be dispensed in an airtight package. In jar formulations that are found in the OTC market, the product is exposed to more air when the jar is opened. This increased air space makes the product at the bottom of the jar turn brown before the jar is empty. Once the HQ has oxidized, it is no longer active and should be discarded.

In prescription HQ formulations, attempts are made to increase the product's potency by adding penetration enhancers (eg, glycolic acid), sunscreens, and tretinoin as a supplemental skin-lightening agent. Other prescription formulations have included microsponges for controlled release of HQ, while others are packaged in a special canister dispenser.

Tretinoin

Topical tretinoin is used both alone and in combination with HQ as a prescription skin-lightening treatment. Tretinoin has been shown to decrease the appearance of cutaneous freckling and lentigines.[3] Irregular grouping and activation of melanocytes accounts for the dyspigmentation associated with photoaging.[4] Normalization of this change has been histologically demonstrated with retinoids.[5] Although the effect is more dramatic with topical tretinoin, topical retinol has been thought to provide similar effects as a cosmeceutical. Retinol may be converted in small amounts to tretinoin in the dermis, accounting for some of the clinical benefit.

Over-the-counter Skin-Lightening Products

The results of prescription skin-lightening therapy can be improved by adding adjunctive cosmeceutical products that incorporate vitamin- and plant-derived ingredients into a moisturizing base, which may be beneficial in improving the skin barrier while adding another mechanism of action for decreasing pigment production. Cosmeceutical skin lighteners should always be applied on top of prescription therapies, as the cosmeceutical moisturizing base may inhibit penetration of the prescription.

The most commonly used ingredient in skin-lightening moisturizers is licorice extract. The botanical actives are known as liquiritin and isoliquertin, which are glycosides containing flavonoids.[6] Liquiritin induces skin lightening by dispersing melanin and typically is applied to the skin in a dose of 1 g daily for 4 weeks to produce clinical results. Irritation is not a side effect, and liquirtin easily can be combined with HQ.

The second most common OTC skin-lightening agent in the United States and the most popular skin-lightening agent in Asia is kojic acid, chemically known as 5-hydroxy-2-(hydroxymethyl)-4-pyranone. Kojic acid is a hydrophilic fungal derivative obtained from the *Aspergillus* and *Penicillium* species.[7] It has been reported that kojic acid is equivalent to HQ in its skin-lightening ability.[8] The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper.

Two other substances that commonly are combined include aleosin and arbutin. Aleosin is a low-molecular-weight glycoprotein obtained from the *Aloe vera* plant. It is a natural hydroxymethylchromone functioning to inhibit tyrosinase by competitive inhibition at the DOPA oxidation site.[9,10] In contrast to HQ, it shows no cell cytotoxicity; however, it has a limited ability to penetrate the skin due to its hydrophilic nature. It sometimes is mixed with arbutin. Arbutin is a naturally occurring gluconopyranoside that causes decreased tyrosinase activity without affecting messenger RNA expression.[11] It also inhibits melanosome maturation. Arbutin is not toxic to melanocytes and is used in a variety of skin-lightening preparations in Japan at a 3% concentration. Higher concentrations are more efficacious than lower concentrations but paradoxical pigment darkening may occur.

Vitamin C is used in some OTC formulations as a skin-lightening active or as an antioxidant or pH adjuster. It can be hard to determine from the jar label its exact role, but if ascorbic acid is listed in the last 3 to 5 ingredients, it probably is not effective for hyperpigmentation. Ascorbic acid interrupts the production of melanogenesis by interacting with copper ions to reduce dopa quinone and blocking dihydrochinindol-2-carboxyl acid oxidation.[12] High concentrations of ascorbic acid might be more effective but will lower the pH of the skin cream, possibly causing irritation.

Summary

Skin lightening for the treatment of lentigines, melasma, and postinflammatory hyperpigmentation is a challenge for the dermatologist. Skin care products can function as adjuncts by increasing tolerability, enhancing efficacy, and providing photoprotection. Prescription treatments can remove existing pigment from the skin, shut down the manufacture of melanin, and prevent the transfer of existing melanin to the melanosomes. There currently are no topical products available to accomplish all 3 of these functions, which provides an opportunity for the effective use of skin care products in the treatment regimen.

References

1. Halder RM, Richards GM. Management of dyschromias in ethnic skin. *Dermatol Ther.* 2004;17:151-157.
2. US Food and Drug Administration. Importation of active pharmaceutical ingredients (APIs) requirements: CPG 460.200 pharmacy compounding compliance policy guides manual (Tab M). http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM118050.pdf. Published March 16, 1992. Updated May 29, 2002. Accessed October 5, 2011.
3. Weinstein GD, Nigra TP, Pochi PE, et al. Topical tretinoin for treatment of photodamaged skin. a multicenter study. *Arch Dermatol.* 1991;127:659-665.
4. Gilchrest BA, Blog FB, Szabo G. Effects of aging and chronic sun exposure on melanocytes in human skin. *J Invest Dermatol.* 1979;73:141-143.
5. Bhawan J, Gonzalez-Serva A, Nehal K, et al. Effects of tretinoin on photodamaged skin. a histologic study [erratum appears in 1991;27:1382]. *Arch Dermatol.* 1991;127:666-672.
6. Amer M, Metwalli M. Topical liquiritin improves melasma. *Int J Dermatol.* 2000;39:299-301.
7. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg.* 1999;25:282-284.
8. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg.* 1996;22:443-447.
9. Choi S, Lee SK, Kim JE, et al. Aloesin inhibits hyperpigmentation induced by UV radiation. *Clin Exp Dermatol.* 2002;27:513-515.
10. Jones K, Hughes J, Hong M, et al. Modulation of melanogenesis by aloesin: a competitive inhibitor of tyrosinase. *Pigment Cell Res.* 2002;15:335-340.
11. Hori I, Nihei K, Kubo I. Structural criteria for depigmenting mechanism of arbutin. *Phytother Res.* 2004;18:475-469.
12. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs 4% hydroquinone in melasma. *Int J Dermatol.* 2004;43:604-607.