ELSEVIER

Seminars in Cutaneous Medicine and Surgery

Treatment of Hyperpigmentation

Heather Woolery-Lloyd, MD,*,† and Jenna N. Kammer, BA‡

Hyperpigmentation is a common dermatologic condition that is seen in all skin types but is most prominent in skin of color. In skin of color, any inflammation or injury to skin can almost immediately be accompanied by alterations in pigmentation, either hyperpigmentation or hypopigmentation. Post-inflammatory hyperpigmentation can be observed in many skin conditions including acne, eczema, and contact dermatitis and treatment can be challenging. The goal is to reduce the hyperpigmentation without causing undesirable hypopigmentation or irritation in the surrounding area. This review will discuss current research on treatments for hyperpigmentation and approaches to treating this condition.

KEYWORDS hyperpigmentation, hydroquinone, dyschromia, ochronosis, melasma

Hyperpigmentation is a common dermatologic condition that is found in all skin types but is most prominent in skin of color. Any inflammation or injury to the skin can almost immediately be accompanied by alterations in pigmentation, either hyperpigmentation or hypopigmentation. Postinflammatory hyperpigmentation appears in many skin conditions, including acne, eczema, and contact dermatitis, and treatment can be challenging. The goal is to reduce the hyperpigmentation without causing undesirable hypopigmentation or irritation in the surrounding area.

A variety of topical agents are available to treat hyperpigmentation. These topical agents can interfere with the pigmentation process at several different levels. The gold standard for treatment is a hydroxyphenolic chemical called hydroquinone. Hydroquinone acts by inhibiting the conversion of dihydroxyphenylalanine to melanin by inhibiting the activity of tyrosinase.[1] Other mechanisms of action include interfering with DNA and RNA synthesis, degrading melanosomes, and destroying melanocytes.[2] Two percent hydroquinone is available over-the-counter in the United States and Canada. Four percent hydroquinone is available by prescription.[3] The Kligman formula combines hydroquinone with a retinoid and a steroid, which enhances efficacy.[3]

A common side effect when one uses hydroquinone to treat dyschromia attributable to acne is the "hydroquinone halo." This occurrence is characterized by a halo of hypopigmentation surrounding the dark macule attributable to the bleaching of the surrounding normal skin. This is frequently observed when patients apply hydroquinone with their fingertips to small macules. More common side effects with hydroquinone include irritation and erythema. When prescribing hydroquinone, one should warn patients of possible irritation and recommend that patients discontinue the treatment if any significant redness or inflammation occurs. Irritation from hydroquinone is frequently caused by the hydroquinone itself or by sodium metabisulfite, a common preservative in hydroquinone preparations.[4] Continued use of hydroquinone when irritation is present may lead to postinflammatory hyperpigmentation.

A rare side effect of hydroquinone is exogenous ochronosis, which is paradoxical darkening of the skin. It usually begins with erythema followed by blue-black patches on the face where the hydroquinone was applied. In severe cases, blue-black macules can progress to papules and nodules on sun-exposed areas after long-term usage of hydroquinone.[5] It may be triggered from inhibition of homogentisic acid oxidase locally by hydroquinone. This rare side effect was common in South Africa, where long-term hydroquinone use was widespread. In the United States, ochronosis is less common; approximately 30 cases have been reported in North America,[3] and typically it occurs with long-term continued use of hydroquinone over decades. This risk may be reduced with sunscreen because the

*Department of Ethnic Skin Care, University of Miami Cosmetic Medicine and Research Institute, Miami Beach, FL.
†University of Miami Department of Dermatology and Cutaneous Surgery, Miami, FL.
‡Drexel University College of Medicine, Philadelphia, PA.
Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Woolery-Lloyd is a shareholder in Sanabella LLC; has been an investigator for Johnson & Johnson, Allergan, Loreal and Galderma; and has received payment for service on speakers' bureaus and serving on the Advisory Boards from Johnson & Johnson and Allergan. Dr Kammer has nothing to disclose.
Address reprint requests to Heather Woolery-Lloyd, MD, University of Miami Department of Dermatology and Cutaneous Surgery, 1295 NW 14th Street, Suite K, Miami, FL 33136. E-mail: woolerylloyd@yahoo.com

1085-5629/11/$-see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.sder.2011.06.004

pattern of ochronosis clinically is photodistributed. Long-term continued use of hydroquinone should be avoided.

For patients with chronic conditions, such as melasma, hydroquinone should be switched to an alternative therapy after a few months or once significant improvement is achieved. There are many alternative agents, and until recently, there were few in vivo trials in which authors examined alternatives to hydroquinone to support claims of efficacy. This article will review alternatives to hydroquinone and will focus on evidenced-based data to support their usage.

Animal, In Vitro, and Open Label Studies

Linoleic Acid

Inhibitors of tyrosinase are believed to suppress melanogenesis and have led to the development of products that use these skin-lightening agents.[6,7] Liposome-encapsulated linoleic acid has demonstrated a whitening effect in ultraviolet (UV)-stimulated hyperpigmented human upper arm skin.[8] In animal studies, investigators evaluated the lightening effects of unsaturated fatty acids on ultraviolet B (UVB)-induced pigmentation of dorsal brown guinea pig skin. All families of unsaturated fatty acids examined inhibited melanin production and tyrosinase activity. Interestingly, linoleic acid was most effective in lightening UVB-induced hyperpigmentation in vivo, whereas α-linolenic acid was most effective in inhibiting melanin production in vitro.[9]

Ellagic Acid and Arbutin

Ellagic acid (EA), an antioxidant, inhibits skin pigmentation resulting from UV irradiation. The results of in vitro experiments indicate that EA suppresses melanogenesis by inhibiting tyrosinase activity. In one study of 30 subjects with melasma authors compared the effects EA, synthetic EA, and arbutin[10] and demonstrated a statistically significant reduction in Mexameter (CK Electronic, Ramstein, Germany) readings in all three groups.

Acerola Fruit Extract

Acerola fruit extract, another tyrosinase inhibitor, has been shown to lighten UVB-induced skin pigmentation in brown guinea pig skin.[11]

Methimazole

Methimazole (1-methyl-2-mercaptoimidazole; MMI) is an oral antithyroid medication that clinically causes hypopigmentation in some patients by inhibiting tyrosinase.[12] A study was conducted with 11 uniformly pigmented guinea pigs treated with MMI topically to one randomly chosen ear for six weeks.[13] The results revealed hypopigmentation in six of 11 MMI-treated sites versus no alterations in any of the control sites.[13]

Blinded Clinical Trials

Dioic Acid

A recent blinded study enrolled 96 Mexican female patients with melasma; one-half of the patients received 1% dioic acid, and the other half received 2% hydroquinone cream.[14] There was a significant improvement in the Melasma Area Severity Index scores from baseline to the end of the study when dioic acid or hydroquinone were used; however, there was no significant difference between the two treatments. In addition, the side effects were similar with both, except pruritus was more common in patients using hydroquinone.

Soy

Soy interferes with melanin transfer by inhibiting the protein-activated receptor 2 (PAR-2) pathway. PAR-2 is a G protein-coupled receptor that controls the ingestion of melanosomes by keratinocytes.[15] Two soybean-derived proteins, namely soybean trypsin inhibitor and the Bowman-Birk inhibitor, interfere with melanosome transfer by inhibiting the PAR-2 activation. The lightening activity of these agents and their ability to prevent UV-induced pigmentation suggests that inhibition of the PAR-2 pathway by soybean extracts may be used as a natural alternative to skin lightening.[16] In a blinded controlled 12-week study, authors evaluated the efficacy of a soy moisturizer containing soybean trypsin inhibitor and Bowman-Birk Inhibitor on 65 women with moderate facial photodamage. There was significant improvement in mottled pigmentation, blotchiness, dullness, fine lines, overall texture, and overall skin tone.[17]

Rucinol

In a prospective, single-center, double-blind, randomized, vehicle-controlled, bilateral (split-face) comparative trial, 32 women with melasma were provided with two identical tubes containing rucinol serum 0.3% or vehicle.[18] Rucinol serum demonstrated significant improvement in melasma when compared with the vehicle control after three months of treatment.

Licorice

Two licorice extracts, glabridin and liquiritin, have demonstrated topical lightening effects. Glabridin is the main active ingredient in licorice extract derived from *Glycyrrhiza glabra* and appears to exert its anti-inflammatory effect via inhibition of superoxide anion production and cyclooxygenase activity. In one in vitro study, authors investigated the inhibitory effects of glabridin on melanogenesis and inflammation by using cultured B-16 murine melanoma cells and guinea-pig skin and found that glabridin inhibits tyrosinase activity in these cells but had no effect on DNA synthesis.[19]

The licorice extract, licochalcone A, is derived from a licorice plant grown in northwest China, *Glycyrrhiza inflata*. Licochalone A has anti-inflammatory as well as antimicrobial effects in randomized vehicle-controlled clinical trials.[20] Topical licochalone A has also demonstrated anti-inflammatory properties by causing a significant reduction in redness

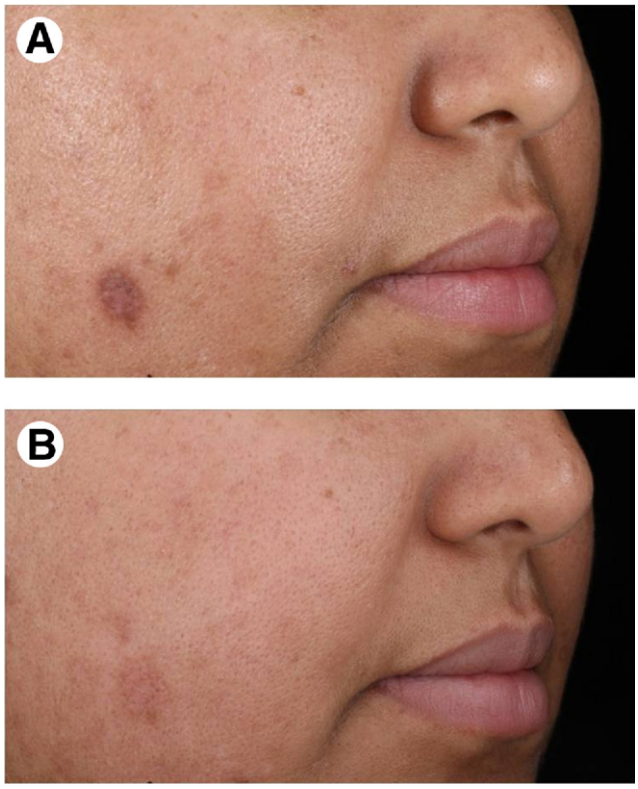

Figure 1 Top: Baseline hyperpigmented macule Bottom: After 6 weeks of treatment with a topical serum containing licorice root extract, retinol and antioxidants.

relative to the vehicle control in both the shave- and UV-induced erythema tests.[20]

In a study of 20 women ages 18-40 years with a clinical diagnosis of bilateral and symmetric idiopathic epidermal melasma, liquiritin cream was applied on one side of the face and a vehicle cream on the other side twice daily for four weeks.[21] Sixteen of the patients were rated as exhibiting an excellent response, with no discernible differences between the normal skin and previously pigmented areas. Two patients showed a fair response, and two showed a good response. In addition, 90% of patients in the liquiritin group showed at least a 75% reduction in lesion size compared to none in the vehicle group.[21] The skin lightening effects of licorice extract is demonstrated in Fig. 1.

Vitamin C

Ascorbic acid (vitamin C) is known to inhibit melanin formation by reducing o-quinone formation. The antioxidant effects of ascorbic acid prevent the production of free radicals, which trigger melanogenesis,[22] and reduce oxidized melanin, changing the pigmentation from black to tan. Moreover, it has a photoprotective effect, by preventing UV-induced free radical damage.[23] Ascorbic acid is retained in the epidermis, which is an advantage over sunscreens because they are easily removed.[24]

A split-face, double-blind study was conducted to evaluate the therapeutic effect of topical 5% L-ascorbic acid versus topical 4% hydroquinone in patients with melasma by the use of colorimetry, digital photography, regular color slides, and subjective evaluations.[25] The best subjective improvement was observed on the hydroquinone side with 93% good and excellent results, compared with 62.5% on the l-ascorbic acid side.[25] However, colorimetric measures demonstrated no statistical differences between the two groups. The lightening effect of hydroquinone was apparent as early as the first month of treatment, whereas that of l-ascorbic acid was not observed until the third month. Although less effective than hydroquinone, patients in the ascorbic acid group experienced fewer side effects. Sixty-eight percent of patients in the hydroquinone group had side effects compared with 6.2% in the ascorbic acid group.[25] Therefore, ascorbic acid may be a good adjunct when treating hyperpigmentation. In addition, the authors suggested that 10% ascorbic acid might be more effective. Further clinical studies are needed to assess the efficacy of ascorbic acid in melasma.

Iontopheresis has been used to enhance epidermal absorption of vitamin C. Twenty-nine female patients with melasma were enrolled in a randomized, double-blind, placebo-controlled study of vitamin C iontophoresis and demonstrated a significant decrease in pigmentation compared to placebo.[26]

N-Acetylglucosamine and Niacinamide

N-acetylglucosamine (NAG) is a monosaccharide derivative of glucose. NAG reduces hyperpigmentation by inhibiting the conversion of protyrosinase to tyrosinase, a key step in the production of melanin.[27] Niacinamide is a biologically active amide of vitamin B3 inhibiting the transfer of melanosomes to keratinocytes.[28] A study with 18 Japanese women revealed the depigmentary effect of niacinamide was not the result of a direct impact on melanin synthesis by melanocytes, but a reduction in melanosome transfer from melanocytes to surrounding keratinocytes.[28] An eight-week, double-blind, randomized, split-face clinical trial showed that 2% NAG reduced the appearance of facial hyperpigmentation, and a combination of 2% NAG with 4% niacinamide demonstrated an even greater improvement.[29]

Decapeptide 12

Decapeptide 12, a synthetic, 10-amino acid peptide, has been investigated for its skin-lightening effects. A split-face, randomized, double-blind and placebo-controlled pilot was performed to determine the effect of twice-daily topical application of this oligopeptide (0.01%).[30] Five participants with moderate, recalcitrant melasma were enrolled in this 16-week study, and all subjects demonstrated statistically significant improvements in the appearance of their melasma and overall facial aesthetics.[30]

Combination Therapy

Some new combination therapies have been introduced that are proven to be as effective as hydroquinone. A combination of glycolic acid, antioxidants and licorice root was shown to be as effective as 4% hydroquinone in an 8-week blinded split-face trial.[31] Another combination of kojic acid, alpha hydroxy acids, and emblica was effective as 4% hydroquinone at 12 weeks.[32]

Combination therapy may provide a new approach to treating hyperpigmentation with significant results.

Chemical Peels

The adjunctive use of chemical peels or microdermabrasion can also be helpful when treating hyperpigmentation. These interventions work best in a series; typically three to five monthly treatments are required to attain the greatest results. Absorption studies prove that these procedures not only remove superficial layers of the stratum corneum but also enhance penetration of topical therapies when treating hyperpigmentation.[33,34] A recent single-blinded randomized study in which the authors compared the therapeutic effects of glycolic acid peels and amino fruit acid peels in patients with melasma illustrated that both are efficacious but amino fruit acid peels were found to be less irritating and better tolerated.[35] Two split-face studies examined a series of four chemical peels with hydroquinone versus hydroquinone alone in 21 women with melasma.[36,37] In one study authors examined salicylic acid peels, whereas in the other they examined glycolic acid peels. Neither study demonstrated a significant difference between chemical peels used with hydroquinone versus hydroquinone alone. However, a larger trial of 40 Indian patients with melasma did demonstrate a statistically significant improvement when chemical peels were added to a modified Kligman daily. In this study a series of six peels were performed every three weeks.[38] The results of these studies suggest that more than four peels may be required to achieve significant results when treating hyperpigmentation.

Treatment Recommendations

When treating hyperpigmentation, it is important to categorize patients into acute or chronic hyperpigmentation. Acute causes, such as acne hyperpigmented macules, can be treated with a Kligman formulation and daily sunscreen to prevent new lesions. In skin of color, a Kligman formula with hydroquinone, 6-8%, tretinoin, 0.025%, and dexamethasone, 0.1% is very effective. Combination therapies with hydroquinone alternatives are also useful as adjunctive therapies. Sunscreens that contain antioxidants and other agents targeting pigment, such as licorice extract and soy, are especially useful to prevent and treat pigment.

For more chronic causes of hyperpigmentation, initial treatment with hydroquinone is useful but alternatives to hydroquinone are essential for maintenance. Hydroquinone should be used for one to three months and then as needed. During "hydroquinone holidays," alternatives should be used once or twice daily for best results. Many of the agents discussed in this review, such as licorice extract, soy, *emblica,* and niacinamide, can be used to maintain patients while off hydroquinone.

Hyperpigmentation can be a common, yet challenging, sequelae of cutaneous inflammation, especially in those with darker skin. Post inflammatory hyperpigmentation and melasma are difficult conditions for many patients generating a negative impact on their quality of life. There are many safe and effective agents available, including a variety of topical skin-lightening products. In addition, procedures, such as chemical peels can serve as adjuncts to topical therapy. Newer combination therapies have provided novel and effective treatment options for hyperpigmentation. More research is needed to identify additional agents that achieve the same, if not better efficacy of hydroquinone with fewer side effects.

References

1. Palumbo A, d'Ischia M, Misuraca G, et al: Mechanism of inhibition of melanogenesis by hydroquinone. Biochim Biophys Acta 1073:85-90, 1991
2. Jimbow K, Obata H, Pathak MA, et al: Mechanism of depigmentation by hydroquinone. J Invest Dermatol 62:436-449, 1974
3. Halder RM, Richards GM: Topical agents used in the management of hyperpigmentation. Skin Ther Lett 9:1-3, 2004
4. Huang PY, Chu CY: Allergic contact dermatitis due to sodium metabisulfite in a bleaching cream. Contact Dermatitis 56:123-124, 2007
5. Lawrence N, Bligard CA, Reed R, et al: Exogenous ochronosis in the United States. J Am Acad Dermatol 18:1207-1211, 1988
6. Akiu S, Suzuki Y, Asahara T, et al: Inhibitory effect of arbutin on melanogenesis-biochemical study using cultured B16 melanoma cella. J Dermatol 101:609-613, 1991
7. Kahn V: Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase. Pigment Cell Res 8:234-240, 1995
8. Shigeta Y, Imanaka H, Ando H, et al: Skin Whitening Effect of linoleic acid Is Enhanced by liposomal Formulations. Biol Pharm Bull 27:591-594, 2004
9. Ando H, Ryu A, Hashimoto A, et al: Linoleic acid and alpha-linolenic acid lightens ultraviolet-induced hyperpigmentation of the skin. Arch Dermatol Res 290:375-381, 1998
10. Ertam I, Mutlu B, Unal I, et al: Efficiency of ellagic acid and arbutin in melasma: A randomized, prospective, open-label study. J Dermatol 35:570-574, 2008
11. Hanamura T: Skin lightening effect of polyphenol extract of Acerola fruit on UVB induced pigmentation. Biosci Biotechnol Biochem 72: 3211-3218, 2008
12. Kasraee B, Handjani F, Parhizgar A, et al: Topical methimazole as a new treatment for postinflammatory hyperpigmentation: Report of the first case. Dermatology 211:360-362, 2005
13. Kasraee B: Depigmentation of brown Guinea pig skin by topical application of methimazole. J Invest Dermatol 118:205-207, 2002
14. Tirado-Sánchez A, Santamaría-Román A, Ponce-Olivera RM: Efficacy of dioic acid compared with hydroquinone in the treatment of melasma. Int J Dermatol 48:893-895, 2009
15. Babiarz-Magee L, Chen N, Seiberg M, et al: The expression and activation of protease-activated receptor-2 correlate with skin color. Pigment Cell Res 17:241-251, 2004
16. Paine C, Sharlow E, Liebel F: An alternative approach to depigmentation by soybean extracts via inhibition of the PAR-2 pathway. J Invest Dermatol 116:585-595, 2001
17. Wallo W, Nebus J, Leyden JJ: Efficacy of a soy moisturizer in photoaging: A double-blind, vehicle-controlled, 12-week study. J Drugs Dermatol 6:917-922, 2007
18. Khemis A, Kaiafa A, Queille-Roussel C, et al: Evaluation of efficacy and safety of rucinol serum in patients with melasma: A randomized controlled trial. Br J Dermatol 156:997-1004, 2007
19. Yokota T, Nishio H, Kubota Y, et al: The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 11:355-361, 1998
20. Kolbe L, Immeyer J, Batzer J, et al: Anti-inflammatory efficacy of licochalcone A: Correlation of clinical potency and in vitro effects. Arch Dermatol Res 298:23-30, 2006
21. Amer M, Metwalli M: Topical liquiritin improves melasma. Int J Dermatol 39:299-301, 2000
22. Catani MV, Rossi A, Costanzo A, et al: Induction of gene expression via activator protein-1 in the ascorbate protection against UV-induced damage. Biochem J 15:77-85, 2001
23. Dreher F, Maibach H: Protective effects of topical antioxidants in humans. Curr Probl Dermatol 29:157-164, 2001
24. Darr D, Combs S, Dunston S, et al: Topical vitamin C protects porcine

skin from ultraviolet radiation-induced damage. Br J Dermatol 127:247-251, 1992
25. 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 43:604-607, 2004
26. Huh CH, Seo KI, Park JY, et al: A randomized, double-blind, placebo-controlled trial of vitamin C iontophoresis in melasma. Dermatology 206:316-320, 2003
27. Bissett DL, Farmer T, McPhail S, et al: Genomic expression changes induced by topical N-acetyl glucosamine in skin equivalent cultures in vitro. J Cosmet Dermatol 6:232-238, 2007
28. Hakozaki T, Minwalla L, Zhuang J, et al: The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. Br J Dermatol 147:20-31, 2002
29. Bissett DL, Robinson LR, Raleigh PS, et al: Reduction in the appearance of facial hyperpigmentation by topical N-acetyl glucosamine. J Cosmet Dermatol 6:20-26, 2007
30. Hantash BM, Jimenez F: A split-face, double-blind, randomized and placebo-controlled pilot evaluation of a novel oligopeptide for the treatment of recalcitrant melasma. J Drugs Dermatol 8:732-735, 2009
31. McDaniel DH, Wu J: Efficacy of a natural-based bleaching cream versus hydroquinone 4% bleaching gel in the treatment of hyperpigmentation. Cosmet Dermatol 21:596-602, 2008
32. Draelos ZD, Yatskayer M, Bhushan P, et al: Evaluation of a kojic acid, emblica extract, and glycolic acid formulation compared with hydroquinone 4% for skin lightening. Cutis 86:153-158, 2010
33. Lee WR, Shen SC, Kuo-Hsien W, et al: Lasers and microdermabrasion enhance and control topical delivery of vitamin C. J Invest Dermatol 121:1118-1125, 2003
34. P, Rajan PE: Grimes Skin barrier changes induced by aluminum oxide and sodium chloride microdermabrasion. Dermatol Surg 28:390-393, 2002
35. Ilknur T, Biçak MU, Demirtaşoğlu M, et al: Glycolic acid peels versus amino fruit acid peels in the treatment of melasma. Dermatol Surg 36:490-495, 2010
36. Hurley ME, Guevara IL, Gonzales RM, et al: Efficacy of glycolic acid peels in the treatment of melasma. Arch Dermatol 138:1578-1582, 2002
37. Kodali S, Guevara IL, Carrigan CR et al: A prospective, randomized, split-face, controlled trial of salicylic acid peels in the treatment of melasma in Latin American women. J Am Acad Dermatol 63:1030-1035, 2010
38. Sarkar R, Kaur C, Bhalla M, et al: The combination of glycolic acid peels with a topical regimen in the treatment of melasma in dark-skinned patients: A comparative study. Dermatol Surg 28:828-832, 2002; discussion: 832