

## Editorial

# Treatment of hyperpigmentation disorders

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Hyperpigmentation is a common and distressing problem which is frequently encountered in dermatology practice. Females report much more with this complaint, although this disorder is not rare in males. The disease has tremendous psychological impact especially in females. Due to their over anxious natures the ladies have tried various beauty creams and treatments before coming to the dermatologists. The hopes are always very high and the demand is always for a rapid cure. In many patients the injudicious use of medicated and cosmetic creams have resulted in many side effects such as acne, hirsutism, erythema, skin thinning and sometimes aggravation of skin pigmentation. At that time it is always very difficult to treat such patients, particularly in dark-skinned individuals. The type of skin, treatments used, duration of the disease and psychological impact on the patient must all be considered before embarking upon the treatment. The goal is to reduce the hyperpigmentation without causing any undesirable side effects.

The most commonly used treatment is topical hydroquinone. Other phenolic agents, such as N-acetyl- 4-

cystaminyphenol (NCAP) are currently being studied and developed. The non-phenolic agents, including tretinoin, adapalene, topical corticosteroids, azelaic acid, arbutin, kojic acid, and licorice extract, are also being used in hyperpigmentation disorders.

Sun exposure often reverses the results of therapy, compromising the lengthy treatment process. Consequently, the first line of therapy for hyperpigmentation is a broad-spectrum sunscreen used in conjunction with a phenolic agent or a non-phenolic agent. There are hundreds of sunscreen formulations with different UV absorbing chemicals in various concentrations.<sup>1</sup> The UVB and UVA absorbing chemicals used in the formulation of topical sunscreens include para-amino-benzoic acid related products, salicylates, cinnamates, benzophenones, zinc oxide, and titanium oxide. Almost all sunscreen products contain a mixture of one or more UVB absorbing chemicals.<sup>1</sup> The efficacy of a sun block is judged by its sun-protection-factor (SPF). The commercially available products are available from SPF 30-60. The higher the SPF, the more effective is the product in countering the side effects of UV light. The selection of base is also important. Patients having oily skin, especially young patients with acne, may be prescribed lotions and those who have normal or dry skin may be advised creams.

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Hydroquinone has been the gold standard for treatment of hyperpigmentation for over 50 years. It is a hydroxyphenolic compound which acts by inhibiting the enzyme tyrosinase, thereby reducing the conversion of DOPA to melanin. Some of the other possible mechanisms of action are the destruction of melanocytes, degradation of melanosomes and inhibition of the synthesis of DNA and RNA. Hydroquinone is commercially available as 2% and 4% concentrations. Antioxidants, such as vitamin C, retinoids or alpha-hydroxy acids may be used as additives to increase penetration and enhance efficacy. Exogenous ochronosis with the use of hydroquinone is a rare complication. It has been reported in dark-skinned patients, who frequently use very high concentrations of hydroquinone over large surface areas.<sup>2</sup> Other adverse reactions include irritant and allergic contact dermatitis, and nail discoloration. Post-inflammatory hyperpigmentation may occur from the contact dermatitis. Hypopigmentation of the normal skin surrounding the treated areas may also occur. These complaints are resolve with discontinuation of the hydroquinone.<sup>3</sup>

Monobenzone, monobenzyl ether of hydroquinone, is a special topical phenolic agent, which is used only in vitiligo patients involving more than 50% of the body surface area. This drug can achieve depigmentation of the normal skin surrounding vitiliginous. The cream is applied in a thin layer, rubbed into the normally pigmented areas two or three times daily. Depigmentation is usually achieved after 6-12 months with 20% monobenzone

cream. It should then be applied only as often as required to maintain depigmentation. Monobenzone cream can produce satellite depigmentation at sites distant from the site of initial application.

N-acetyl-4-cysteaminylphenol (NCAP) is another phenolic agent that is currently being developed and is not yet available for general use. NCAP acts to decrease intracellular glutathione by stimulating pheomelanin rather than eumelanin.<sup>4</sup> It also inhibits tyrosinase activity, has been found to be more stable, and causes less irritation than hydroquinone. In a retrospective study of 12 patients with melasma using 4% NCAP, 66% showed marked improvement, and 8% showed complete loss of melasma lesions.

Kojic acid (5-hydroxy-2-(hydroxy methyl)-4-pyrone) is a naturally occurring hydrophilic fungal derivative evolved from certain species of *Acetobacter*, *Aspergillus* and *Penicillium*. This compound is currently gaining popularity in the treatment of hyperpigmentation disorders.<sup>5</sup> It acts by inhibiting the production of free tyrosinase with efficacy similar to hydroquinone. In Japan, kojic acid has been increasingly used in skin care products. This is because, until recently, topically applied kojic acid at 1% concentration had not exhibited any sensitizing activity.<sup>6</sup> However, more recent long-term Japanese studies have shown that kojic acid has the potential for causing contact dermatitis and erythema.<sup>6</sup>

Arbutin, which is the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound that has been used for post-inflammatory

hyperpigmentation.<sup>7</sup> The action of arbutin is dependent on its concentration. Higher concentrations are more efficacious than lower concentrations. A dose-dependent reduction in tyrosinase activity, as well as melanin content in melanocytes, is demonstrated. It may cause a paradoxical hyperpigmentation.<sup>7</sup> In comparative *in vitro* studies of various compounds used to improve the appearance of disorders of hyperpigmentation, arbutin was found to be less toxic than hydroquinone.

Licorice extract is not yet available in North America, but has been used in other parts of the world, particularly in Egypt. Its mechanism of action is similar to that of kojic acid. The main component of the hydrophobic fraction of licorice extract is glabridin, which has an effect on the skin. Studies investigating the inhibitory effects of glabridin on melanogenesis and inflammation have shown that it inhibits tyrosinase activity of melanocytes. No effect on DNA synthesis was detectable.

The efficacy of topical tretinoin 0.05-0.1% as monotherapy for post-inflammatory hyperpigmentation has been reported.<sup>8</sup> Tretinoin was also used as monotherapy in a study on 38 African-American patients with melasma and 68%-73% of patients improved. In 88% of the patients, moderate side-effects of desquamation and erythema were observed.<sup>9</sup> Darker skinned patients who develop dermatitis from tretinoin may develop post-inflammatory hyperpigmentation secondary to the dermatitis. The mechanism of action of tretinoin in the treatment of melasma is poorly understood. Clinical improvement has been found to be associated with a

reduction in epidermal melanin, possibly as a result of the inhibition of tyrosinase.<sup>10</sup> Although tretinoin can be effective as monotherapy for hyperpigmentation and melasma, it requires 20-40 weeks of treatment. Tretinoin can also be used in conjunction with hydroquinone or other depigmenting agents to improve their efficacy. The first published study using a combination of tretinoin 0.1%, hydroquinone 5%, and dexamethasone 0.1% appeared in 1975.<sup>11</sup> Tretinoin is shown to reduce the atrophy of the corticosteroid and facilitated the epidermal penetration of the hydroquinone. The irritation induced by tretinoin is reduced by the corticosteroid. The first triple combination topical therapy approved by the US FDA for melasma comprises of fluocinolone acetonide, hydroquinone 4% and tretinoin 0.05%. In studies of patients with melasma, 78% had complete or near clearing after 8 weeks of therapy. Similar results and favorable safety profile were seen in a 12-month study.<sup>12</sup> In a randomized clinical trial, the efficacy of adapalene 0.1% was found to be comparable to that of tretinoin 0.05% cream in the treatment of melasma (mainly epidermal type). The results showed that there were fewer side-effects and greater acceptability among patients using adapalene.<sup>13</sup>

It may be concluded that the treatment of hyperpigmentation disorders is a long process. The psychosocial impact of these disorders should be taken into consideration. There are several topical treatment options available, the most common of which is hydroquinone. The use of combination therapy and monotherapy with non-phenolic agents is gaining popularity. These treatment options are primarily for epidermal disorders

of hyperpigmentation. Dermal disorders of hyperpigmentation are difficult to treat, and have not been effectively managed using currently available treatments.

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