Depigmenting and Bleaching Agents: Coping with Hyperpigmentation

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Since the introduction of hydroquinone as a skin-lightening agent in 1961, several products with bleaching properties have been used for the treatment of pigmented disorders of the skin. The most important medical indications for the use of these agents are melasma and postinflammatory hyperpigmentation, although they have also been used as alternative options for the treatment of ephelides, solar lentigines, nevi, and lentigo maligna. This article reviews the most commonly used bleaching agents, discusses their mechanism of action, and focuses on their efficacy and safety in treating unwanted skin pigmentation.

Based on our current knowledge, the ideal bleaching agent has to fulfill certain pharmacologic criteria. It should have a potent bleaching effect with a rapid time of onset (less than 2 to 3 months), carry no short- or long-term side effects, and lead to a permanent removal of undesired pigment. Most of the currently available bleaching or depigmenting agents cause a temporary removal of hyperpigmentation, which usually recurs after discontinuation of therapy. Presently, there are three categories of bleaching agents (Table 1): phenolic compounds, nonphenolic compounds, and combination formulas.

Phenolic Compounds

These chemical compounds contain a phenol group. The most important agent of this group is hydroquinone (HQ), which is considered the most commonly prescribed bleaching agent today. HQ derivatives are the monobenzyl ether of hydroquinone, the 4-methoxyphenol, the 4-isopropylcatechol, the 4-hydroxyanisol, and the N-acetyl-4-S-cystaminylphenol.

Hydroquinone

HQ, a hydroxyphenolic chemical compound, inhibits the conversion of dopa to melanin by inhibiting the tyrosinase enzyme. It may also function by interfering with the formation or degradation of melanosomes and by inhibiting the synthesis of DNA and RNA within melanocytes. Its chemical resemblance with certain melanin precursors (tyrosine and dihydroxyphenylalanine) explains its ability to be metabolized in melanocytes as well as its selective action on melaninogenesis. Unlike the monobenzylether of hydroquinone, HQ is not metabolized to cytotoxic free radicals and, therefore, is not a melanocidal agent. The depigmented effects are limited to the site of application and are usually reversible, although some investigators claim that HQ can cause permanent or vitiligo-like hypopigmentation, especially in darker skin types.

HQ affects only cells with active tyrosinase activity, such as epidermal melanocytes. It is less effective in conditions where dermal melanin predominates, as the latter is usually stored within macrophages (melanophages) that have little or no tyrosinase activity.

A number of clinical studies have established the beneficial therapeutic effect of HQ in the treatment of melasma and other pigmentary disorders. In summary, 2% HQ was reported to produce a decrease in hyperpigmentation, which was evaluated as good to excellent in 14–70% of treated patients. Higher concentrations of HQ appeared to be more effective but were associated with augmented side effects, mainly irritation at the application sites. Combined preparations containing HQ and other agents, particularly tretinoin and glycolic acid, appear to be more effective. The combination of 4% HQ and 2% glycolic acid in a single cream improved the photodamaged areas of the neck and upper chest, including pigmentary changes, in 19 women after twice daily application for 12 weeks.

The bleaching effect of HQ is usually seen after a few weeks to a few months of daily application. Its efficacy as a depigmenting agent depends on several parameters, such as its concentration, its chemical stability, and the vehicle used. In general, the higher the concentration, the more effective and the more irritant HQ becomes. At a concentration of 4–5%, HQ formulations are considered to be very effective, although they can have a significant irritant effect. Concentrations above 5% and up to 10% can be used for more refractory cases and are usually compounded with nonfluorinated steroid creams with or without the additional use of salli-
clic acid or tretinoin. Most commercially available formulations in Europe contain 2% of HQ, which is considered safe and effective. Many dermatologists, however, may choose to begin treatment with higher HQ concentrations and use a 2% concentration as maintenance therapy.

A number of different vehicles can be used for HQ formulations, although several clinical studies have suggested a hydroalcoholic vehicle as more suitable, e.g., equal parts of propylene glycol and absolute ethanol. The addition of antioxidants, such as ascorbic acid or sodium bisulphate, enhances the stability of hydroquinone as it can be easily oxidized—even in a tube or bottle—and become ineffective.

The side effects of hydroquinone can be categorized as acute and chronic. Acute side effects include allergic and irritant contact dermatitis, nail discoloration, and postinflammatory hyperpigmentation. High concentrations of HQ (above 5 to 6%) have been associated with persistent hypopigmentation or depigmentation, a condition that has been termed “leukoderma en confetti.” Exogenous ochronosis is the most important chronic side effect of HQ. It presents in the form of reticulated, ripplelike, sooty pigmentation affecting common sites of HQ application, such as the cheeks, the forehead, and the periorbital areas. Histologically these lesions show banana-shaped yellow-brown pigment globules in and around collagen bundles in conjunction with giant cells and melanophage-containing granulomas in the upper dermis. These pigmentary changes are irreversible and there is no effective treatment. The cause of ochronosis is unknown, but there is a strong correlation between the occurrence of this condition and the duration of HQ application. In an epidemiological study that was conducted in South Africa, there were no cases of exogenous ochronosis observed after application duration of less than 6 months, whereas there was an incidence rate of 92% in individuals who used the product for more than 16 years. These data have raised concern about the long-term safety of HQ, especially in the context of chronic unsupervised use of over-the-counter, high-concentration products. Even the 2% concentration of HQ contained in most commercially available formulations may carry a small, yet considerable risk of this irreversible exogenous pigmentation. For these reasons, the use of HQ has been banned in Japan and has been severely restricted in South Africa and Europe.

Contraindications of HQ use include a proven allergy to the agent and past therapeutic resistance. It is not known whether the drug is able to pass the placenta and, thus, most physicians do not recommend the use of HQ during pregnancy or lactation.

**Monobenzyl Ether of Hydroquinone**

The monobenzyl ether of hydroquinone (MBEH), also known as monobenzone, has a similar mechanism of action to HQ on pigmented cells. Moreover, MBEH is subjected to selective uptake by melanocytes and is metabolized into reactive free radicals that are capable of permanently destroying melanocytes. This explains why MBEH causes permanent depigmentation, even after discontinuation of its use. Interestingly, the loss of pigmentation is also observed at sites distant to the site of MBEH application. For this reason, MBEH is primarily used as an agent for generalized depigmentation in patients with extensive vitiligo. The process of depigmentation is long and may require 9 to 12 months of daily application to achieve total depigmentation. Mild irritation usually occurs during application.

**Other Phenolic Compounds**

Additional phenol compounds are now used in many countries; for example 4-methoxyphenol, which is usually applied as a 20% cream for the depigmentation of vitiligo universalis and has a similar mechanism of action to MBEH. 4-isopropylcatechol and 4-hydroxyanisole are cytotoxic to pigmented cells and show variable results in the treatment of pigmented disorders. Recently, a combination product of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin was tested in a double-blind multicenter study and was found to improve significantly the solar lentigenes and related hyperpigmented lesions of the face and hands after a twice-daily application of up to 24 weeks. Finally, N-acetyl-4-S-cystaminylphenol is a phenolic-thio-ether that acts as a substrate for tyrosinase and selectively targets cells with active melanin synthesis. It is much more stable and less irritant than hydroquinone. In a study of 12 patients with melasma, N-acetyl-4-S-cystaminylphenol produced marked improvement or complete clearing with minimal side effects in 75% of cas-

**Table 1. Main Categories of Bleaching or Depigmenting Agents**

<table>
<thead>
<tr>
<th>Phenolic compounds</th>
<th>Nonphenolic compounds</th>
<th>Combination formulas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinone</td>
<td>Azelaic acid</td>
<td>Kligman’s formula</td>
</tr>
<tr>
<td>Monobenzyl ether of hydroquinone</td>
<td>Tretinoin</td>
<td>Pathak’s formula</td>
</tr>
<tr>
<td>4-methoxyphenol</td>
<td>L-ascorbic acid</td>
<td>Westerhof’s formula</td>
</tr>
<tr>
<td>4-isopropylcatechol</td>
<td>Kojic acid</td>
<td></td>
</tr>
<tr>
<td>N-acetyl-4-S-cystaminylphenol</td>
<td>N-acetylcystein</td>
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es. The long-term side effects of the above compounds are unknown, largely because of the limited experience in their use.

B Nonphenolic Compounds

Azelaic Acid

Azelaic acid (AZA) is a naturally occurring 9-carbon dicarboxylic acid that was isolated recently from cultures of Pityrosporum ovale and was associated with the hypomelanosis seen in tinea versicolor. It has been shown to have beneficial therapeutic effects in acne vulgaris and certain pigmentary disorders, such as melasma and lentigo maligna. AZA interferes with the function of tyrosinase in vitro and may also inhibit DNA synthesis and mitochondrial oxidoreductase. It does not appear to affect normal melanocytes, and treatment of constitutively pigmented normal skin, freckles, lentigines, and nevi with AZA did not produce a significant therapeutic result. The drug, however, appears to exert an antiproliferative and cytotoxic effect on hyperactive and abnormal melanocytes and may halt the progression of lentigo maligna to lentigo maligna melanoma.

AZA has been used at concentrations of 15–20% for the treatment of melasma and postinflammatory hyperpigmentation. In double-blind comparative studies, topical AZA achieved a good-to-excellent response in 60–70% of melasma patients, and was found to be more effective than 2% HQ and of equivalent efficacy to 4% HQ. A combination regimen of AZA with topical tretinoin 0.05% for the treatment of melasma produced similar results after 6 months compared with AZA monotherapy (approximately 73% of good-to-excellent response). In double-blind comparative studies, the addition of tretinoin was associated with an earlier and more pronounced lightening (VC-PMG), was used in a 10% cream base and produced a significant lightening effect in 19 of 34 patients with melasma ( arbitration of the o-quinones of DL-DOPA, norepinephrine, and dopamine to their corresponding melanin. AsA esters have been tested in an effort to overcome this problem. A stable derivative of AsA, magnesium L-ascorbyl-2-phosphate (VC-PMG), was used in a 10% cream base and produced a significant lightening effect in 19 of 34 patients with melasma after 3 months of twice daily application.

Kojic Acid

Kojic acid (5-hydroxy-2-hydroxymethyl-4-H-pyran-4-one) is a fungal metabolic product that is structurally related to maltol. It is a potent tyrosinase inhibitor and functions by chelating copper at the active site of the enzyme. It also acts as an antioxidant and prevents the conversion of the o-quinones of DL-DOPA, norepinephrine, and dopamine to their corresponding melanin. Kojic acid is used in a 1–4% cream base, alone or in combination with tretinoin, hydroquinone, and/or a corticosteroid. It appears to act synergistically with glycolic acid. The addition of 2% kojic acid in a gel containing 10% glycolic acid and 2% HQ was superior to the same gel without kojic acid in improving the epidermal melasma of 40 women after 12 weeks of treatment. Compared with 2% HQ, kojic acid alone appears to be less effective. There are scant data from the literature with regard to its long-term side effects, al-
though some investigators have reported a high frequency of contact sensitivity to this product.39

Combination Formulas

The above agents have been used in combination formulas with the purpose of augmenting the efficacy of each of these separate active ingredients, of shortening the duration of therapy and of reducing the risk of adverse effects. In general, combination therapies have a more effective bleaching effect than monotherapies and most physicians commence treatment with one of these formulas applied once daily (at night) and continue with 2% HQ treatment for maintenance. The most commonly used combination formulas are listed in Table 2.

Kligman’s Formula

Kligman and Willis used a combination regimen of 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone in a hydrophilic ointment and demonstrated an efficacy in the treatment of melasma, ephelides, and postinflammatory hyperpigmentation. In this formula, tretinoin functions as an irritant to facilitate epidermal penetration of HQ, and it also plays an antioxidative role to prevent oxidation of HQ. Dexamethasone, on the other hand, is used to decrease the irritation caused by HQ or tretinoin and to inhibit melanin synthesis by decreasing cellular metabolic activity. Depigmentation occurs rapidly beginning within 3 weeks after twice-daily application of the formula and maximizing in 5 to 7 weeks.

Pathak’s Formula

Pathak and colleagues conducted a clinical trial of this formula on 300 Hispanic women with melasma and showed superior results with creams or lotions that contained 2% HQ and 0.05–0.1% tretinoin. The authors suggested that topical steroids are not necessary to achieve rapid clearance and that they should be preserved for patients who suffer irritation from tretinoin or HQ.

Westerhof’s Formula

The combination of 4.7% N-acetylcystein (NAC), 2% HQ, and 0.1% triamcinolone acetonide improved melasma after 4 to 8 weeks of application in a left–right, placebo-controlled clinical study of 12 female patients.40 The bleaching effect of NAC probably relates to the increase of intracellular glutathion that stimulates phaeomelanin rather than eumelanin synthesis after binding with dopaquinone, clinically producing a lighter pigment. As sulfur-containing moeties, NAC and glutathion exert an inhibitory effect on tyrosinase, which may also account for their bleaching properties.

There are several variations of the above combination formulas that pertain to the concentration of the different ingredients and the type of topical steroid. For example, the use of a lower concentration of tretinoin (0.05%) and the substitution of dexamethasone with 1% hydrocortisone acetate or 0.1% betamethasone valerate in Kligman’s formula reduces the tretinoin-induced irritation and diminishes the risk of steroid side effects that are often seen with fluorinated steroids, e.g., telangiectasia, atrophy, or hypertrichosis.41

Basic Principles of Bleaching Therapy

Pretreatment Considerations

Before initiating therapy with bleaching agents, physicians should inform patients that the treatment is directed toward improving pigmentation rather than resolving its cause. Patients should also be instructed that the results will not be permanent and that, despite initial improvement, recurrence of the hyperpigmentation can occur after a period of time. In this case, the bleaching treatment may need to be repeated in the future. It is also important to define the nature and anatomic localization of the pigmentedary process before starting patients on bleaching therapy. Melasma and postinflammatory hyperpigmentation may occur in the epidermis, dermis, or both. The Wood’s light examination can help locate the site of pigmentation, as it intensifies epidermal pigment but not dermal pigment. However, it is not always a reliable method, particularly in black skin where the differentiation between epidermal and dermal pigment can be rather difficult. The most reliable method is a skin biopsy, which determines histologically the cause of the pigment disorder and the depth of melanin deposition. The latter is probably the most important factor in determining therapeutic responses to bleaching therapy. Epidermal pigmentation as well as certain types of mixed dermal/epidermal pigmentation respond favorably to topical bleaching therapy, while dermal pigmentation is usually resistant to depigmented agents and requires other therapeutic options, e.g., lasers or camouflage.

Table 2. Bleaching Formulas

<table>
<thead>
<tr>
<th>Name of formula</th>
<th>Active ingredients</th>
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| Kligman’s formula | Hydroquinone 5%  
Tretinoin 0.05–0.1%  
Dexamethasone or betamethasone valerate 0.1% |
| Pathak’s formula | 2% HQ  
Tretinoin 0.05–0.1% |
| Westhorf’s formula | N-acetylcysteine 3%  
HQ 2%  
Hydrocortisone 1% |
General Measures

The success of topical bleaching therapy largely depends on patient compliance and the avoidance of factors that can provoke cutaneous hyperpigmentation. The avoidance of sun exposure is essential to prevent the stimulatory effect of ultraviolet light on melanogenesis. Sun protection can be achieved using appropriate clothing as well as a potent sun block with a sun protection factor (SPF) of at least 15 to 30. Sunscreen application should be continued even after the cessation of therapy and/or the disappearance of skin pigmentation due to the risk of pigment recurrence.

The role of sex hormones such as estrogens and progesterone in the pathogenesis of melasma has been well established. There is no consensus, however, of whether oral contraceptives should be discontinued, mainly because of the lack of strong evidence that stopping them or changing to a lower concentration contraceptive regimen will significantly alter the clinical outcome of melasma.

In patients with postinflammatory hyperpigmentation, topical steroids represent important adjuncts of the therapeutic regimen. They are used to treat the underlying inflammatory reaction. Hydrocortisone, triamcinolone acetonide, or betamethasone valerate are the most widely used corticosteroids that can be prescribed alone or in combination bleaching formulas.

Duration of Therapy

Because of the risk of exogenous ochronosis, any bleaching product should be used for no longer than 2 years. If there is no improvement after 6 months of application, the use of bleaching agents should be stopped and alternative modalities should be pursued.

Combined Use with Chemical Peeling

Bleaching agents can be combined with superficial or medium-depth chemical peels, such as 50–70% glycolic acid or 30% trichloroacetic acid peels. HQ or a combined regimen of HQ, tretinoin, and a topical corticosteroid can be used before and/or after a chemical peel to augment the therapeutic response and decrease the risk of postinflammatory hyperpigmentation that is frequently seen in melasma patients.42

Conclusions

A fair number of bleaching agents is presently available to treat hyperpigmentation disorders. Although beneficial for many patients, the majority of these medications do not permanently eliminate the abnormal pigmentation and are frequently associated with significant side effects. Each patient should be assessed individually and a risk/benefit ratio should be established for each therapeutic approach.

References

21. Schallreuter KU, Wood JM. Azelaic acid as a competitive