Skin bleaching: highlighting the misuse of cutaneous depigmenting agents

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Abstract

Hydroquinone and other cutaneous depigmenting agents are widely used by dermatologists to treat pigmentary disorders. On 29 August 2006, the US Food and Drug Administration (FDA) published a monograph in the US Federal Register proposing to ban all hydroquinone products that have not been approved via a New Drug Application process. Reports in the scientific literature about the occurrence of exogenous ochronosis, in relation to the use of hydroquinone, was one of the concerns expressed by the FDA in relation to this agent. However, a review of the English-language scientific literature reveals that most of the reported cases of hydroquinone-induced exogenous ochronosis occurs in Africa, where the cultural practice of skin bleaching is highly prevalent. Skin bleaching, the practice of applying hydroquinone and/or other depigmenting agents to specific or widespread areas of the body, is a dangerous practice associated with a diverse range of side-effects, including mercury poisoning. Thus, this current discussion within the dermatological community on the safety of hydroquinone provides a unique opportunity to raise awareness about skin bleaching.

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Keywords
corticosteroids, depigmenting agents, hydroquinone, skin bleaching

Introduction

The US Food and Drug Administration (FDA) Over-the-Counter Miscellaneous Panel had designated 2% as a safe concentration for hydroquinone products until 29 August 2006, when the FDA published a monograph in the US Federal Register proposing to ban all hydroquinone products that have not been approved via a New Drug Application process. This proposal arose following the failure of manufacturers to comply to a request by the FDA for safety studies on hydroquinone. In addition, the FDA has cited many safety concerns about this product, including the occurrence of hydroquinone-induced ochronosis. Nonetheless, hydroquinone remains a popular agent for the treatment of pigmented disorders in people with skin phenotypes IV to VI. Thus, the proposal to ban this agent has prompted many within the dermatological community to publish articles that address the concerns of the FDA. One important point highlighted in some of these published articles is that hydroquinone-induced ochronosis occurs typically in Africa, where the cultural practice of skin bleaching is prevalent. Thus, this current discussion within the dermatological community about the safety and regulation of hydroquinone is a perfect opportunity to present an overview of the practice of skin bleaching, and to raise more awareness about the occurrence and dangers of this practice.

Skin bleaching is the practice by which depigmenting agents are used typically by people with skin phenotypes IV to VI on a cosmetic basis, primarily to lighten normally dark skin. The practice of skin bleaching dates back over many years in different communities around the world. In fact, in the early 1900s some US physicians advocated the use of radiation therapy as a skin bleaching agent. Despite the initial early enthusiasm for this treatment, the many undesirable side-effects of this therapy became apparent, leading to an end to this dangerous practice. Currently, skin bleaching remains a common part of life within some African communities, reflected even by the local vernacular. For example, in Mali and Senegal, the term caco and xeesal are, respectively, used to describe this practice, while in Ghana, the term nensoeben is used to describe the ochronosis that develops as a side-effect of this practice.

Interviews conducted on skin bleachers in sub-Saharan African countries highlights many factors driving this practice. A desire to lighten skin colour is cited as a primary motivating factor for skin bleaching. This is because in some countries, white skin is still perceived to be associated with social privileges, including better job and marital prospects. However, some skin bleachers may not desire white skin, but instead desire radiant skin. Up until recent years there was limited choice with regard to the types of cosmetic products available in Africa and Europe, especially for individuals with Fitzpatrick skin phenotype VI. In absence of such products, bleaching the skin may be perceived as an alternative method of enhancing one’s beauty, especially prior to important social events. Other reasons cited by individuals partaking in skin bleaching include imitation of others and dependency on the products. Finally, the higher prevalence of dyschromias in people with skin phenotypes IV to VI may be another factor that initiates, promotes, and/or excuses this practice. As a result of a lack of understanding about the appropriate use of depigmenting agents, coupled with negative cultural perceptions about dark
Prevalence of skin bleaching
A review of the scientific literature demonstrates that individuals from diverse communities around the world, including Africa, North America, Europe, Asia and the Middle East practice skin bleaching. Evidence from the non-medical press further highlights the global burden of this practice. Thus, scientific studies conducted on the practice of skin bleaching, as summarized in Tables 1 and 2 and discussed in detail below, may only represent the clinical iceberg of a more widespread problem.

Africa
The worldwide awareness of the cultural practice of skin bleaching originates from the work of Findlay et al., who in 1975 first reported on the occurrence of exogenous ochronosis in South African women. These women had used high concentrations (3.5–7%) of hydroquinone-containing agents over the course of many years for bleaching their skin. Skin bleaching remained a problem in South Africa and by 1986 the total sales volume of skin lighteners was an estimated 30 million pounds. Currently, skin bleaching continues to have an impact on dermatological practice in many sub-Saharan African communities, with prevalence rates of this practice in community and clinic settings documented to be between 26% and 67%. This estimate is based on descriptive studies and surveys on the cosmetic use of cutaneous depigmenting agents conducted in community- and/or hospital-based settings via questionnaires and/or interviews. In fact, most of the knowledge acquired about the practice and complications of skin bleaching originates primarily from such studies performed in sub-Saharan African countries. However, a review of some of these studies reveals inherent limitations. First, since most of the studies are based on interviews and/or questionnaires, the study subjects may have given inaccurate histories about their cosmetic use of cutaneous depigmenting agents. Second, studies in hospital-based settings may overestimate the prevalence of skin bleaching, as individuals attending dermatology clinics are more likely to have primary dermatological problems for which they would have sought out cutaneous depigmenting agents. Interestingly, studies also reveal that individuals often...
<table>
<thead>
<tr>
<th>Reference (country of origin and type of study)</th>
<th>Prevalence of adverse reaction</th>
<th>Infections</th>
<th>Dyschromias</th>
<th>Systemic side-effects</th>
<th>Other side-effects</th>
<th>Motivation for skin bleaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajose (Nigeria, community study)</td>
<td>50%</td>
<td>Not specified</td>
<td>Yellowish brown discoloration of skin</td>
<td>Haematuria</td>
<td>Striae; hirsutism; pedema; thinning of the skin; easy bruising; body odour; weight gain</td>
<td>(1) Treatment of skin blemishes. (2) To become more attractive and satisfy the desires of opposite sex. (3) Fashionable trend.</td>
</tr>
<tr>
<td>Ajose (Nigeria, hospital study)</td>
<td>69.2%</td>
<td>Not specified</td>
<td>Mycoses; scabies; warts; erysipelas; pyodermas</td>
<td>Ochronosis; confetti-like hypomelanosis</td>
<td>Hyperpigmentation</td>
<td>(1) To even out skin tone. (2) To lighten complexion. (3) To improve appearance of skin prior to an event. (4) Dependency.</td>
</tr>
<tr>
<td>Faye et al. (Mali, hospital study) Del Giudice et al. (Senegal, hospital study) Ly et al. (Senegal, hospital study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
</tr>
<tr>
<td>Mahé et al. (Senegal, hospital study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Hyperchromia; hypochromia; ochronosis; blue ear</td>
<td>Hyperpigmentation of face</td>
<td>Increased compared to non-steroid users; occurrence of mild vaginal bleeding; lower placental weight; lower plasma cortisol</td>
</tr>
<tr>
<td>Mahé et al. (Senegal, hospital study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
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<td>Nnoruka et al. (Nigeria, hospital study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Macular hyperpigmentation of face</td>
<td>Diabetes; hypertension</td>
<td>Not specified in study</td>
</tr>
<tr>
<td>Pett et al. (France, hospital study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Hyperpigmentation of face</td>
<td>Biological signs of adrenal suppression</td>
<td>Not specified in study</td>
</tr>
<tr>
<td>Pitché et al. (Togo, community study)</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Acne; cutaneous atrophy</td>
<td>Not specified in study</td>
</tr>
<tr>
<td>Traore et al. (Burkina Faso, community study)</td>
<td>55.5%</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Not specified in study</td>
<td>Acne; cutaneous atrophy; vibices; telangiectasia eczema; burn</td>
<td>(1) Change skin colour. (2) Change skin texture. (3) Imitation of others. (4) No reason given. (5) Imperfections treatment.</td>
</tr>
</tbody>
</table>

Table 2 An overview of studies conducted worldwide on the cosmetic use of depigmenting agents (adverse reactions and motivation for skin bleaching)
continue their practice of skin bleaching throughout pregnancy and lactation. For example, Mahé et al. \(^2\) demonstrated that 68.7% of selected women between 6 and 9 months gestation, attending a maternity centre in Dakar, Senegal, used skin lighteners for cosmetic purpose during their pregnancy. This included agents containing hydroquinone, highly potent corticosteroids and products of unknown composition. Interestingly, some of the women in this study reported starting or increasing their use of skin lighteners because of their pregnancy.

**North America**

To date, there have been no formal studies conducted in North America to assess the prevalence of skin bleaching. This indicates that either this practice is uncommon or it is under-recognized by practicing physicians in North America. Nonetheless, an insight on the cosmetic use of depigmenting agents in North America can be gained by reviewing case reports and other studies documenting adverse reactions to these agents. This review provides conflicting results.

In a review of the 789 worldwide reported cases of exogenous ochronosis, only 22 cases (1983–2006) occurred in the USA. \(^3\) Subjects from the USA with hydroquinone-induced ochronosis had often self-medicated with these agents as a mode of therapy for their primary dyschromias. This indicates that the cultural practice of skin bleaching, as a mode of changing normal skin colour, is not very common in the USA. However, in the mid-1990s, following an index case of mercury poisoning associated with the use of a Mexican ‘beauty cream’ containing high levels of mercury, a survey was conducted to describe the demographics and patterns of use of this cream in border communities of Arizona, California, New Mexico and Texas. \(^24,25\) The results of this study demonstrated that the majority of users of this ‘beauty cream’ were Hispanic women, with 44% using this ‘beauty cream’ as a skin lightener. Most cream users used this agent over a median of 4 years, with 52% applying this cream two to three times per day. Although most cream users had purchased the cream from Mexico, 21% purchased the cream in the USA, typically at flea markets or herb shops. Although cream users were not asked their motivation for using this agent as a skin lightener, the results of this study do indicate that the practice of skin bleaching may be a problem in some communities within the USA. Thus, further studies to investigate the motivations for the cosmetic use of cutaneous depigmenting agents are warranted in the USA. This is of particular importance given the fact that the demographics of the USA is changing, with a higher proportion of the US population predicted to be of African and Hispanic descent in the future.\(^1\)

**Europe**

The practice of skin bleaching has been reported in Africans and Afro-Caribbeans living in European countries, including the United Kingdom and France. \(^26\) In fact, the over-the-counter use of hydroquinone has now been banned in Europe, although this agent and various other depigmenting agents remain available illegally in many markets in Europe. \(^2\) In a multicentre study conducted in the Paris region, it has been estimated that 16% to 28% of adult African women seeking dermatological treatment in Paris are regular users of skin bleaching agents. \(^26\) Moreover, in a recent study by Petit et al. \(^27\) on 46 subjects from various African countries attending a dermatology clinic in Paris for side-effects of skin lighteners, 31% had begun their practice of skin bleaching in France.

**Asia**

Ashikari \(^28\) when writing on the Japanese culture, states that since the late 1980s, consumption of ‘whitening’ cosmetics has remained at consistently high levels and a ‘white’ complexion has been considered trendy and desirable in Japan, being a symbolic physical characteristic for identifying Japanese people. Despite the popularity of skin bleaching in Japan, to date there have been no formal studies reported in the English-language scientific literature on the prevalence of this practice in this country. However, there are studies reported in the English-language scientific literature that gives an insight into the practice of skin bleaching in Hong Kong. Tang et al. \(^29\) reported the case of a woman who developed minimal change nephropathy as a complication of the use of mercury containing skin-lightening cream. Furthermore, following an index case of mercury poisoning, a survey was conducted in Hong Kong to describe the demographic characteristics, patterns of use and other laboratory parameters in people who had used the same skin whitening cream. Of note, among 314 cream users, 27% were using it as a skin whitening agent. \(^30\) The motivation for this behaviour was not discussed in this study.

**The Middle East**

To date, there are no formal studies documenting the prevalence of skin bleaching in this region of the world. However, in a study undertaken in Saudi Arabia to investigate the mercury content in skin-lightening creams, Al-Saleh et al. \(^31\) state that in Saudi markets ‘a wide variety of different brands of skin-lightening creams are available, either being imported from overseas or being manufactured locally by traditional herbalists’. This high supply indicates that there may be a high demand for such skin-lightening products in this country.

**Adverse effects of skin bleaching agents**

A diverse range of products at various concentrations are used for skin bleaching. This includes hydroquinone, hydroquinone derivatives (hydroquinone monobenzylether and monomethylether), potent steroids, \(^1\) mercurials (mercuric iodide 1–3% or mercuric chloride 6–
In 2001, Karamagi et al. reported the case of a young black woman with chronic symmetrical sensorimotor polyneuropathy and autonomic neuropathy, which improved 4 months after she stopped the use of hydroquinone-based skin bleaching agents. Although most metabolic factors that may have accounted for her signs and symptoms were excluded, the authors did not perform HIV serological testing on their patient. Thus, the association of her symptoms and signs with her use of hydroquinone was circumstantial.

Exogenous ochronosis (Fig. 1), characterized by progressive asymptomatic hyperpigmentation with associated papules on sun-exposed skin, is another reported side-effect of hydroquinone. Histology of lesional skin demonstrates collagen and elastic fibre degeneration and deposition of ochre-coloured fibres in the dermis. A total of 789 cases of exogenous ochronosis have been reported in the scientific literature, of which 756 occurred in Africa, where the practice of skin bleaching is highly prevalent, suggesting a link between skin bleaching and this side-effect. However, caution should be used when interpreting these data due to the presence of confounding factors that may account for higher levels of exogenous ochronosis in Africa. First, the concomitant use of antimalarials (which may also give rise to ochronosis) are frequently not cited in studies on the complications of skin bleaching. Second, in most studies in Africa on skin bleaching, the diagnosis of ochronosis is often based on clinical assessment, with no lesional biopsies undertaken to confirm these clinical findings. This is understandable in view of the limited resources in Africa, where most of these studies have been conducted. Finally, the
lack of sunscreen use during skin bleaching, the use of higher concentrations of hydroquinone formulations, and the use of formulations containing resorcinol and other agents may all contribute to increase the risk of exogenous ochronosis in relation to the practice of skin bleaching. However, given that over the course of many years, many individuals have been exposed to hydroquinone (it has been available in over-the-counter formulation since about 1956 in the USA), the comparatively low rates of reported exogenous ochronosis, is somewhat reassuring, indicating that this may be an uncommon side-effect of hydroquinone. Alternatively, this low rate may also be a result of under-reporting of this complication in the scientific literature.

Another important theoretical side-effect associated with skin bleaching with hydroquinone agents is the development of cutaneous and internal malignancies. Hydroquinone is a metabolite of benzene, a leukaeogenic agent. It is also associated with the development of mononuclear cell leukaemia in female rats exposed to oral hydroquinone over a 2-year period. Despite this theoretical risks, studies indicate that comparatively low levels of hydroquinone are absorbed with topical application of these agents. Moreover, hydroquinone and its derivative, arbutin (which is hydrolysed to hydroquinone in an acidic environment such as the stomach), are ubiquitous agents, such that humans are exposed to them from consumption of products such as tea, coffee, rice, onions, cranberries, blueberries and wheat. Furthermore, since hydroquinone is important in the development of black and white films, individuals working in this industry have high exposures to this agent. Nonetheless, studies that have assessed mortality rates and cancer prevalence in such individuals have not identified a higher-risk profile in this cohort. In light of the above, we can conclude that there remains a lack of conclusive evidence supporting a carcinogenic risk from the topical use of hydroquinone. Alternatively, since the practice of skin bleaching involves the application of high concentrations of hydroquinone over widespread areas of the body, it may be argued that this may represent a higher-risk profile for the development of malignancies. However, only two cases exist in the literature that documents the development of cutaneous malignancy in relation to skin bleaching. In these cases, spindle cell squamous cell carcinomas occurred in association with skin bleaching with hydroquinone agents. The mechanism for this observation is postulated to be through the pro-carcinogenic effect of hydroquinone or due to suppression of the natural photo-protection effect of melanin. Further studies are warranted in skin bleachers to accurately assess their risk of cutaneous malignancies.

Corticosteroids

Topical steroids are anti-inflammatory agents used for the treatment of many inflammatory skin diseases. They are popular cutaneous depigmenting agents used for skin bleaching, and it is the present authors’ opinion that the extensive use of illegal clobetasol-containing agents is responsible for most of the severe side-effects associated with skin bleaching in Francophone countries. Their effect as depigmenting agents is mediated via the initial local vasoconstriction occurring when applied to the skin, giving an impression of an immediate reduction in pigmentation of the skin. Eventually, topical steroids exert their depigmenting effect via an inhibitory effect on epidermic melanogenesis. Their prolonged use (> 3 weeks), especially on thin skin such as facial and flexural sites, is associated with a range of adverse effects.

This includes the development of striae (Fig. 2), peri-oral dermatitis, rosacea-like eruption, acne vulgaris, telangiectasia, poor wound healing, easy bruising and hypertrichosis. Other side-effects include ophthalmic problems (cataracts, glaucoma, eye infections and blindness) associated with the application of topical steroids to the face, especially the eyelids and aseptic osteonecrosis (personal observations). Cutaneous infections (Fig. 3), such as dermatophytosis, cellulitis, erysipelas, scabies and warts, may also occur as a complication of the misuse of topical steroids. Often there is an atypical presentation or a masking of the clinical presentation of these cutaneous infections. For example, Mahé et al. reported the case of a young black woman, who used 0.05% clobetasol propionate and hydroquinone on the peri-lesional skin of a hypochromic region on her cheek. Over time, this masked the hypochromic lesion on her cheek, which was one of the presenting features of her paucibacillary leprosy. Finally, the use of potent topical steroids is associated with systemic side-effects including diabetes and hypertension, Cushing’s syndrome, immunosuppression and adrenal insufficiency.
Mercury salts produce their cutaneous depigmenting effect via inhibition of melanin formation. This occurs because mercury salts compete with copper in tyrosinase. Historically, chronic mercury poisoning has occurred in the context of industrial exposure (felt hat industry) or during the use of mercurial medicinal preparations (used in the past to treat infectious skin disorders such as syphilis and impetigo). Currently, skin lightening is also a cause of mercury toxicity. The features of mercury toxicity, also known as the ‘hatters disease’, as immortalized in Alice in Wonderland by Lewis Carroll, consists of psychiatric (disturbance of recent memory, impairment of intellectual function, inattention and depression) and neurological (irritability, memory loss and neuropathies) problems. Other adverse reactions noted with mercury toxicity includes renal impairment (minimal change or membranous glomerulonephritis) and a paradoxical increase in skin pigmentation. The latter occurs either by an increase in melanin production (mechanism unknown) or via direct deposition of metallic mercury granules in the dermis. The percutaneous absorption of mercury occurs exclusively via cutaneous appendages and, hence, on lesional biopsy, peri-follicular accentuation of mercury deposition is observed in mercury-induced hyperpigmentation. Interestingly, the use of mercurial agents for skin lightening by pregnant and/or lactating women has also been associated with adverse effects in their neonates, including the development of anaemia, renal impairment and cataracts.

Figure 3 Tinea inguinalis due to Trichophyton rubrum in a 40-year-old man from Central Africa. Note the surrounding hypopigmented skin, a result of the practice of skin bleaching.

Other depigmenting agents
Other agents used during skin bleaching include kojic acid and glycolic acids. Kojic acid works primarily as a tyrosinase inhibitor and an antioxidant. It is derived from various fungal species, including Aspergillus and Penicillium. Side-effects observed with this agent include irritant contact dermatitis. Glycolic acids are alpha-hydroxyl acids derived from sugar cane. At low concentrations, it has an epidermal discohesive effect, while at high concentrations it results in epidermolysis. Both these actions lead to removal of the superficial layers of the epidermis and, hence, a depigmenting effect when used for skin lightening. Additional possible mechanisms for depigmentation include acceleration of keratinocytic turnover with a reduction in their melanosome loading time. Side-effects observed with this agent include irritant contact dermatitis, with the risk of post-inflammatory hyperpigmentation.

Conclusion
The current focus within the dermatological community on the safety and regulation of hydroquinone presents a unique opportunity to raise awareness on the occurrence and dangers of skin bleaching. Aesthetic and systemic side-effects of skin bleaching not only remain a public health problem in most parts of sub-Saharan Africa, but also may increasingly impact many other communities around the world. It is important that we educate individuals with pigmentory problems to seek early dermatological care for their dermatoses, rather than to self-medicate with over-the-counter or illegally obtained cutaneous depigmenting agents. However, this would not be enough to reduce the global burden of skin bleaching. Instead, a multifaceted approach is required, addressing several issues concurrently. First, more studies in the field of human sciences, to consider the sociological and psychological factors that are responsible for the search of a lighter complexion (which may vary among different communities) are required to guide the development and implementation of appropriate public health prevention campaigns. Second, international cooperation between governmental, non-governmental and medical agencies is required to decrease the international trafficking of illegal depigmenting agents, especially clobetasol-containing products. Third, continued rigorous scientific studies, especially in Western, Arab and Asian countries where such studies remain scarce, are required to critically evaluate the global burden and adverse health effects associated with skin bleaching. Finally, more research directed towards the
development of alternative safer agents for the inhibition of skin pigmentation is required.

**Key points**

- Skin bleaching is the use/mis-use of depigmenting agents: the primary objective being to lighten normally pigmented skin.
- Individuals from diverse communities around the world practise skin bleaching.
- A wide range of agents such as hydroquinone and its derivatives, steroids, mercury compounds, kojic acid, alpha hydroxy acids, plant-derived products and even hydrogen peroxide are used for skin bleaching.
- Many adverse effects have been reported in association with skin bleaching.
- A multi-faceted approach is required to reduce the global burden of skin bleaching.

**References**

5. Boston Globe. Can the Ethiopian change his skin or the leopard change his spots: radium light turns Negro’s skin white. 25 January 1904.
6. New York America. Burning out birthmarks, blemishes of the skin and even turning a Negro white with the magic rays of radium, the new mystery of science! 10 January 1904.
42. Tobin AM, Arraghy J, Kirby B, O’Shea L. Adrenal suppression following topical use of clobetasol propionate illegally supplied as a bleaching agent. *Ir Med J*


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