HYDROQUINONE

Dr. Charlene DeHaven, M.D.
Clinical Director, INNOVATIVE SKINCARE®

Topical hydroquinone is used frequently throughout the world as a skin bleaching agent. Hydroquinone for cosmetic use is chemically synthesized. It may be found in concentrations up to 15% or more but a doctor’s prescription is required by the FDA (United States) for preparations containing concentrations above 2%. The CIR Expert Panel states hydroquinone should not be used in “leave-on” cosmetic formulations. In spite of this, internet sites can easily be found that offer topical hydroquinone in concentrations over 2% and very commonly as high as 4% or more.

The World Health Organization of the United Nations states: “It is recommended that over-the-counter sales of creams containing hydroquinone be restricted. Health education programs should be developed to discourage the use of hydroquinone-containing creams…”

Hydroquinone was originally introduced many years ago as a less toxic alternative to mercury-based bleaching agents, which were extremely toxic. Attention is now being focused on the potential toxicities and adverse effects of hydroquinone itself.

MECHANISM OF ACTION
Hydroquinone is easily absorbed into the skin and its absorption increases dramatically when alcohols are present in a topical preparation. Hydroquinone reacts with the functional parts of individual cells and affects cellular metabolism. Hydroquinone has cytotoxic (cell-killing or cell-damaging) activity on the pigment-producing cell of the skin, the melanocyte, as well as on many other cell types. The cell-toxic activity of hydroquinone is caused by a free-radical oxidation mechanism. Free radical development has the potential to damage the melanocyte on its own and may also damage neighboring cells or their physical structures.

Because this free-radical effect also harms the genetic material within the pigment-producing cell, it can result in the development of a cancerous (malignant) cell.

COMPARISON WITH OTHER AGENTS
Arbutin, which is of plant origin, decreases the production of the skin pigment melanin. Arbutin inhibits an enzyme called tyrosinase which is required for one of the chemical steps in melanin formation. This inhibition of pigment formation occurs without cytotoxic (cell-damaging) activity.

Kojic acid, of plant origin and an alpha-hydroxy acid, is another enzyme inhibitor of tyrosinase. It decreases pigment production in a manner similar to arbutin. Adding both kojic acid and arbutin to a product causes a potentiation of the lightening effects from both, particularly when the product is used during daytime hours.

Laser treatments have been used for pigmentation irregularities but require a surgical procedure and have their own list of potential complications. Laser treatments should be administered under the direction of a physician regarding risks and benefits.

The skin’s pigmentation process may be modified by affecting any step in the pigmentation process. Several of these steps involve the melanocyte but there are several other required steps independent of the melanocyte. The single intended site of action of hydroquinone is its cytotoxic effect on the melanocyte. In addition to damaging or killing the melanocyte, hydroquinone also induces considerable secondary inflammation on surrounding skin structures.

POTENTIAL ADVERSE EFFECTS
It was once thought that concentrations of hydroquinone of 2% or less had negligible potential for adverse effects. We now know this is not true, as the medical literature reports problems occurring with lesser
concentrations. The topical side effects after hydroquinone application are thought to be related to its mechanism of cytotoxicity. Another earlier myth was that only heavily pigmented skin suffered from adverse effects related to hydroquinone use. This also is untrue, as side effects in Asians, Hispanics, Caucasians and Blacks with less pigmentation have been reported in the medical literature. Applying hydroquinone to skin and then exposing the skin to sunlight markedly increases potential toxicity. Additionally, hydroquinone is systemically absorbed through the skin with measurable amounts appearing in urine after topical application. Orally ingested hydroquinone is very rapidly absorbed by the GI tract and is known to incite kidney and liver damage. In the presence of moisture and at room temperature, hydroquinone metabolizes to quinone which can cause serious issues such as eye irritation, leading to conjunctivitis (red eye) and erosions of the cornea (open sores over the central eye). The potential adverse effects involving inflammation (redness) and cell damage (related to free radical damage) potentially result in severe reactionary hyperpigmentation. The potential development of malignant cells is also of great concern.

Inflammation
Redness (also called erythema), an indicator of inflammation, reliably occurs with exposure to hydroquinone in concentrations of 2% up to 5% in a tested population when applied 5 days per week for 13 weeks. This redness dissipates after the treatment is stopped but the skin has suffered the effects of inflammation during the exposure period. Visible inflammation is found in the majority of users with any concentration of hydroquinone. Since the substance is toxic to cells, even if redness cannot be seen with the naked eye, there is ongoing inflammation accompanying the cell damage associated with the substance. This is a type of irritant dermatitis, or skin inflammation caused by an irritating substance.

Irritant or Allergic Dermatitis
This is an allergic response to a substance to which the skin has become sensitized. It may begin with an inflammatory response but the subject can become sensitive to the product that they develop skin inflammation when only a tiny amount of substance is applied to the skin or even if previously compatible substances are applied.

Systemic Absorption
Hydroquinone is readily absorbed through the skin and can be detected in urine as the intact parent substance (rather than a metabolite) after the 2% cream is applied. The evidence relating to kidney damage of orally ingested material raises concerns here, considering that hydroquinone applied to the skin must get through the blood stream and the rest of the body in order to be found in urine. This raises other questions about the cancer-causing (malignant) potential and other cell-damaging (cytotoxic) properties of hydroquinone that could occur with systemic absorption (passage through the skin to the remainder of the body). Blood cell toxicity and leukemia have been associated with hydroquinone absorbed throughout the body.

Dyschromia
A literal translation of this term would be “abnormal discoloration”. Even though hydroquinone is applied for skin bleaching, its end result can be the formation of large patches of uneven skin color. Dyschromia is very unsightly and difficult to treat. Since hydroquinone has itself been the cause of the dyschromia it is not an effective treatment. Laser treatment is sometimes prescribed but is not always effective, requires a surgical procedure, and has its own potential complications.

Exogenous Ochronosis
This is a type of dyschromia that is particularly serious. Furthermore, it is usually impossible to control once it has developed. Another variant of this skin pigment disorder is inherited and can be associated with malignancies, but this exogenous (meaning ‘caused outside the body’) type is associated with topical hydroquinone use. It involves increased pigmentation of any skin exposed to hydroquinone. The majority of patients suffering from ochronosis have heavier genetic melanin production. Ochronosis is especially frequent in South African Blacks, who sometimes use as high as...
27% concentration of hydroquinone in skin bleaching products. This disorder can also occur in Asians, Hispanics and Caucasians with hydroquinone use. Treatment is extremely frustrating because improvement occurs so slowly or not at all with this debilitating condition. The photo below illustrates the debilitating and permanent effects of ochronosis.

Macular hyperchromia, a type of ochronosis shown in the photo above, is an increased pigmentation of the area surrounding the eyes. It occurs in up to one-third of African Blacks using hydroquinone skin-bleaching products. Improvement in this condition is extremely slow.

Striae
Striae are the “stretch marks” that often occur with pregnancy and rapid weight gain. Their appearance has also been associated with the use of hydroquinone. They are permanent and result from skin inflammation and resultant scarring related to hydroquinone use.

Very Rapid Re-Pigmentation
This condition described in the medical literature relates to the disease vitiligo that very rapidly re-pigments after the use of hydroquinone is discontinued. Vitiligo is a skin disorder manifested by areas devoid of pigment that appear as very pale skin pigmentation mixed with normally pigmented areas. A common treatment is to apply skin bleaching agents to the normally pigmented skin encouraging loss of melanin and a blending with the depigmented skin. Improvement may occur but is very rapidly lost within a few weeks as the skin rapidly re-pigments.

Fingernail Discoloration
Fingernails may develop a brownish discoloration with 4% hydroquinone-containing skin bleach that also contains tretinoin. When use of the cream is stopped, the nail discoloration may gradually go away.

Hydroquinone Neuropathy
A single case report in the medical literature involves the gradual development of increasing weakness in the legs associated with topical hydroquinone use. This patient used 2 hydroquinone bleaching preparations for about 4 years. She stopped using the creams and 4 months later, her leg weakness resolved.

CURRENT USE
Topical hydroquinone in concentrations in excess of 4% can still be found on black markets particularly in the developing world. Hydroquinone is prescribed by physicians in the United States and other countries, especially in combination with topical steroids which are hoped to lessen the side effect profile. Most physicians prescribe hydroquinone for brief use and expect it will be used by the patient on a temporary basis. However, it can be difficult for the patient to transition off of hydroquinone without return of pigmentation or development of reactionary hyperpigmentation. This is especially problematic for the hydroquinone user when the regimen is not physician-guided. Because of this and the other factors previously discussed herein, both consumers and professionals are much more interested in non-hydroquinone lightening products.


“DNA-Protein Crosslink and DNA Strand Break Formation in HL-60 Cells Treated with
Trans,Trans-Muconaldehyde,Hydroquinone and their Mixtures”, RP Amin, G Witz; Int J Toxicol; 2001

“Exogenous Ochronosis. An Update on Clinical Features, Causative Agents and Treatment Options”, CY Levin,

“Skin Diseases Associated with the Cosmetic Use of Bleaching Products in Women from Dakar, Senegal”, A Mahe,


“Nail Staining from Hydroquinone Cream”, SM Ozluer, J Muir;

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