Hydroquinone: hero or villain?

Hidroquinona: vilã ou heroína?

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Autor:
Leandra d'Orsi Metsavaht[1]

[1] Dermatologist and executive director of the Instituto

ABSTRACT

Hydroquinone has been used as a whitening agent for more than 50 years, however its safety and toxicity have been questioned in the last two decades. In the present literature review, it is possible to verify that its carcinogenic and mutagenic potential in humans has not been proven to date. In addition, the population is in fact much more exposed to hydroquinone than commonly perceived, via both cosmetic compounds (e.g. hair dyes) and foods (e.g. pear, beverages and coffee). Therefore, prescribing hydroquinone as a depigmenting agent in concentrations of up to 4% is safe and devoid of systemic consequences.

Keywords: hydroquinone; toxicity; melanosis; safety

RESUMO

A hidroquinona é usada como agente clareador há mais de 50 anos, e, nos últimos 20, suas segurança e toxicidade têm sido questionadas. Nesta revisão bibliográfica, pode-se verificar que seu potencial carcinogênico e mutagênico não foi comprovado até hoje em humanos. Além disso, estamos muito mais expostos à hidroquinona do que imaginamos, tanto em compostos cosméticos (por exemplo, tinturas de cabelos) quanto em alimentos, como a pera, bebidas e o café. Portanto, sua prescrição como despigmentante em concentrações de até 4% é segura e sem consequências sistêmicas.

***Palavras-chave**: hidroquinona; toxicidade; melasma; segurança*

Correspondence to:
Leandra d'Orsi Metsavaht
Rua Visconde de Pirajá 407/905 /Ipanema 22410-003 – Rio de Janeiro-RJ
E-mail: leandra@metsavaht.com.br

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INTRODUCTION

Hydroquinone is an aromatic phenolic compound used as a bleaching agent for over 50 years. It is also present in cosmetics, such as hair dyes, with multiple roles when in low concentrations (up to 2%); as an antioxidant, fragrance and inhibitor of polymerization. It is also used as a reducing agent for photography manufacturing. Like this, it is present in the everyday life of a large part of the population, mainly for women. Hydroquinone's toxicology and safety have been investigated since 1986 by the Cosmetic Ingredient Review (CIR). The target for the reviews is its carcinogenic potential. According to the assessment performed by the **International Agency for Research on Cancer (IARC)** in 1999 on its carcinogenic risk in humans, hydroquinone is not classifiable according to its carcinogenicity to humans (Group 3).[1] In a study about its safety in 2006, Nordlund et al demonstrated that there is no malignancy risk and that the risk for ochronosis is low when used with a medical prescription and surveillance.[2]

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HISTORY

Hydroquinone's bleaching effect was first observed in cats by Oettel in 1936. In the 1950s, the substance was used as a sunscreen and its bleaching effect was seen randomly. Not too long after, it was available in some places in the USA as a topical agent, when its bleaching effect in human skin was noted. Spencer, in 1961, performed the first study using hydroquinone in the concentrations of 2.3 and 5% twice a day for 3 months on the dorsum of the hands of Caucasian men with solar lentigos. He noticed that the results were dose-de- pendent, with recurrence upon discontinuation. In 1998, in a non-randomized study of the use of hydroquinone 4% with a broad-spectrum sunscreen, 89.5% of patients improved. In 2000, Ennes et al. conducted a comparative study of hydroquinone 4% with placebo for the treatment of melasma, and found that 38% had a complete preliminary response against 8% of the patients on placebo.[3]

PHARMACOLOGY

Hydroquinone (1,4 dihydroxybenzene) is a phenolic derivative that acts inhibiting tyrosinase, possibly through the connection with this enzyme or the interaction with copper molecules in its coupling site, leading to a change in the melanosome and an increase of its destruction, besides also a possible inhibition of the DNA and RNA synthesis.[3]

HYDROQUINONE ABSORPTION

We can assume the exposure to hydroquinone throughout life is not a worrisome issue. Excessive exposure to hydroquinone 4% cream for 6 months (let us say that 6 56.8g tubes have 13.6g of hydroquinone, of which half is absorbed, (a total of 6.8g) is comparable to life-long exposure of hydroquinone in coffee (62g/cup X 1 daily cup X 365 days/year X 40 years = 0.9g) or pears (2500 g/pear X 1 pear/week X 52 weeks/year X 10 years = 1.3g).What can be even more significant is that humans have a baseline excretion of 115.4g/h or 2770g/day of hydroquinone with no exposure to bleaching agents. Over 60 years, this amount reaches 61g of hydroquinone in the urine,that presumably found its way to excretion after systemic exposure, as through food.[4]

HYDROQUINONE TOXICITY AND SAFETY

In the last decade, there has been a great concern about the use of topical hydroquinone due to the lack of clinical studies that fulfill the new federal rules and because of the therapy risks that have been observed. Ochronosis, a blue-white discoloration, has been noticed in dark-skinned individuals from South Africa. In the United States, ochronosis is much less frequent. An explanation for this phenomenon is the fact that hydroquinone in concentrations higher than 8% can be found in OTC products in other countries. This uncontrolled access to high concentrations for a prolonged period can increase the risk of adverse effects related to this medication. Besides, these formulations can contain other substances, such as resorcinol, lime juice, mercury, potash, crushed camphor spheres, peroxides and chlorides, all of which can contribute to the development of ochronosis.[5-8]

In 1982, the Food and Drug Administration (FDA) determined initially that hydroquinone would be safe and effective enough to be sold in the concentrations of 1.5 to 2%. However, in 2006, the FDA announced that they would change their position, indicating that commercially available OTC and prescription products containing hydroquinone that had not been previously studied as drugs, should be submitted along with clinical studies as "new drugs", otherwise they would be removed from the market. The only preparation not affected by this rule is the triple formulation, because it was marketed after investigation with clinical studies.[9,10] There are many reasons for these concerns by the FDA, such as systemic absorption, ochronosis and drug-induced carcinogenesis. The European Union banished hydroquinone from cosmetic products in 2001, even though is it still sold with a medical prescription.[5] One of the concerns with hydroquinone is its potential risk for the production of a Benzene derivative after processing in the liver. These derivatives could cause bone marrow toxicity and could have an antiapoptotic effect. When applied on the skin, however, hydroquinone deviated from the hepatic route, and its main excretion route is through the kidneys, as hydro soluble molecules. Another concern is regarding the risk of development of renal adenoma because of the potentially toxic metabolites. Besides, there are no reports on skin or internal organ cancers with the topical use of hydroquinone since the mid-XX century.[5]

Hydroquinone is a compound commonly found in food and beverages such as coffee, tea, fruits, red wine, wheat and pear skin. A controlled study with workers that deal directly with hydroquinone, either manufacturing the substance or exposed to a large amount, did not show any evidence of premature death or malignancies. Oral or injectable hydroquinone in animals was not shown to be carcinogenic and did not cause any bone marrow changes. In a study about the safety of hydroquinone in 2006, Nordlund et al. demonstrated that there is no risk for malignancy and the ochronosis risk is low if hydroquinone is used with medical prescription and supervision.[2]

HYDROQUINONE EFFICACY

In 1998, Amer assessed the efficacy of hydroquinone 4% in combination with a broad-spectrum sunscreen in patients with different pigmentation disorders. Of the 70 patients in the study, 50 had melasma, 10 freckles, and 10 post-inflammatory hyperpigmentation. The study demonstrated a response that was from good to excellent in 89.5% of melasma patients. These results should be interpreted with no parsimony, since it was not a controlled nor a randomized study. Haddad et al. conducted a randomized, double-blind, controlled study with 30 melasma patients, comparing a skin bleaching complex(*skin whitening complex* - SWC), which the study fails in not informing its components, and hydroquinone 4%. There was an improvement in 76.9% of patients treated with hydroquinone. *Hurley et al.*, tested glycolic acid peel in 21 Hispanic patients, and concluded that monotherapy with hydroquinone 4% combined with daily sunscreen not only improves melasma, but also has a similar efficacy to treat-

ment associated with chemical peel. The use of hydroquinone with a medical prescription has been recommended in the United States in concentrations higher than 2%, applied twice daily. If there is no improvement after 2 months, the recommendation is to discontinue treatment, even though some cases only show improvement after 6 months of use. Most of the adverse effects, such as irritation, erythema and peeling can be associated to the excessive use or misuse of the product, or even to the use of an inappropriate soap or too much rubbing of the skin.[11]

CONCLUSION

American drug regulation laws have gone through changes over the years, imposing safety and efficacy testing to long used drugs, of more than 50 years.

The pharmaceutical industry has no financial interest in funding these studies. The mutagenic and carcinogenic effects of hydroquinone have not been proven till this day. The worse side effect ever published with topical hydroquinone is ochronosis, which is rare in North America, but very common in Africa, where it is marketed in high concentrations, such as 8%, besides being associates to products that also promote this side effect, such as resorcin. The study by Jacob Levitt, published in the Journal of the American Academy of Dermatology in 2007, is largely scientifically based and shows the safety of hydroquinone. Lewitt is a dermatologist and also the vice-president of Taro Pharmaceuticals, which manufactures hydroquinone 4%, and he has openly declared conflict of interests due to the strict regulations in the USA. In face of this review of the publications on hydroquinone safety and toxicity, we can assume that hydroquinone is safe if used in the proper concentration, with medical prescription and supervision. The triple formula with hydroquinone showed proven efficacy and safety in controlled, double-blind, randomized studies. Consider maintenance with low dose hydroquinone and other bleaching agents for the treatment of melasma. ●

DECLARATION OF PARTICIPATION:

Leandra d'Orsi Metsavaht:
Study conception and planning, Preparation and wording of the manuscript, Data collecting, analysis and interpretation

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