Hydroquinone and its analogues in dermatology – a potential health risk

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Summary

Hydroquinone has been used for decades as a skin lightening agent. Since January 1, 2001, its use in cosmetics has been banned. This ban is as a result of mid-term effects such as leukoderma-en-confetti/occupational vitiligo and exogenous ochronosis. However, a recent literature search on hydroquinone as a skin lightening agent suggests that possible long-term effects such as carcinogenesis may be expected as well.

Metabolites of hydroquinone formed in the liver, e.g., p-benzoquinone and glutathione conjugates of hydroquinone, are mainly responsible for this. In the bone marrow, hydroquinone is oxidized into p-benzoquinone because of the high myeloperoxidase activity. Topically applied hydroquinone-containing creams may give rise to accumulation of these compounds, which can cause DNA damage and mutations. They also have the capability to disrupt protective mechanisms, whereby they facilitate further development of cancer. In the bone marrow, long-term effects such as aplastic anemia and acute myeloid leukemias may occur. Most of the evidence stems from research on benzene toxicity, which appears to arise via its metabolite hydroquinone.

There is no report yet demonstrating carcinogenesis resulting from the application of hydroquinone-containing creams. However doctors should be aware of these potential health risks which were up until now disregarded.

Keywords: carcinogenesis, hydroquinone, skin lightening, toxicity

Introduction

Hydroquinone is generally considered a harmless substance, but we are of the opinion that it is a potential time bomb. Hydroquinone has been shown to induce reversible hypopigmentation in man and animals.[1] This is most likely caused by melanocyte destruction, decreased melanosome formation, altered melanosome structure, increased melanosome degradation, and destruction of membranous organelles.[2] Although in the first publication in 1936 the hypopigmenting properties of hydroquinone were alluded to as toxic,[1] it has nevertheless been used for decades in skin lightening formulations for the treatment of hyperpigmentation.[3,4] Acute side effects are not uncommon, especially irritance responses and contact dermatitis to hydroquinone. Since January 1, 2001 hydroquinone use has been forbidden in the EU as an ingredient in cosmetics.[5] The decision made by the EU was based on mid-term side effects, mainly exogenous ochronosis and leukoderma-en-confetti or occupational vitiligo.

Explanatory list of abbreviations:
RB - tumor suppressor gene
P53 - tumor suppressor gene
Bax - protein that induces the leakage of mitochondrial cytochrome C causing the activation of apoptotic proteases
Bcl2 - protein that blocks the function of Bax by bonding to Bax

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Prescription as a medicine is still permitted, despite the fact that hydroquinone has been shown to be a carcinogen and is nephrotoxic in animal studies.[6–8]

The annual production of hydroquinone was 35 000 tons per year worldwide in 1994. The main industrial uses of hydroquinone are, corrosion inhibitor, fixative (graphical industry), substance of polystyrene manufacture, and rubber production. About 0.05% (= 17 500 kg) of the hydroquinone manufactured was used in skin lightening creams.[9] This constitutes 30 million 30-g tubes of 2% hydroquinone cream or 15 million 30-g tubes of 4% hydroquinone cream.

To obtain a clearer view, a literature study was conducted to identify the mechanisms that could explain the potential carcinogenicity of hydroquinone when applied dermally.[10]

The initial focus of this article is on the toxicodynamics. Health risks related to the carcinogens benzene and hydroquinone will also be discussed.

Toxicodynamics of hydroquinone

Exposure

Hydroquinone is normally applied once a day as a 2% cream although formulations up to 10% are used. Most of the time it is applied to the face, treating melasma or postinflammatory hyperpigmentation following acne, but the cream is also used on other body parts, such as hands, arms, and chest as in solar lentigines.

Treating 1–5% of the surface of the body is not unusual. Not for medical but for social reasons, people with a dark complexion, predominantly women, from all parts of the world try to obtain a lighter complexion and often treat the whole body, sometimes for many years.[11–13]

The larger the area of application, the more hydroquinone will enter the body through the skin. The duration of usage is also important. Normally, the effects of the treatment are visible only after 4–6 weeks. It is often recommended not to apply the hydroquinone-containing skin lightening cream for more than 6 months.

Distribution

In case of long-term application, it is interesting to investigate how hydroquinone is absorbed and how the absorbed hydroquinone is metabolized and excreted. Figure 1 shows in a schematic way how uptake, distribution, and biotransformation take place.

Recently, short-term, single dose, *in vivo* experiments were conducted in humans. These experiments showed that hydroquinone was effectively (45% of total dose) and quickly absorbed by the skin (35% of total dose in 1 h) and relatively quickly absorbed into the bloodstream (30% within 1 h). It was also demonstrated that excretion (via urine, 35% after 24 h) is slower than the uptake into the body.[14] If one considers that with normal use the cream is applied every 24 h and that excretion takes approximately 72 h, it is reasonable to assume that accumulation of hydroquinone will occur. After reaching the bloodstream, hydroquinone is present as free hydroquinone (35%) and as reversible bound to protein (35%), the remainder as irreversible bound to protein (10%).[15]

Two significant differences were observed between the two routes of exposure: first, benzene was absorbed more slowly after intradermal injection than after oral gavage, and second, the intradermally dosed mice produced more conjugates of hydroquinone than did the orally dosed mice. These differences in metabolism may be involved in the previously observed differences in hematotoxicity between the two routes of exposure.[16]

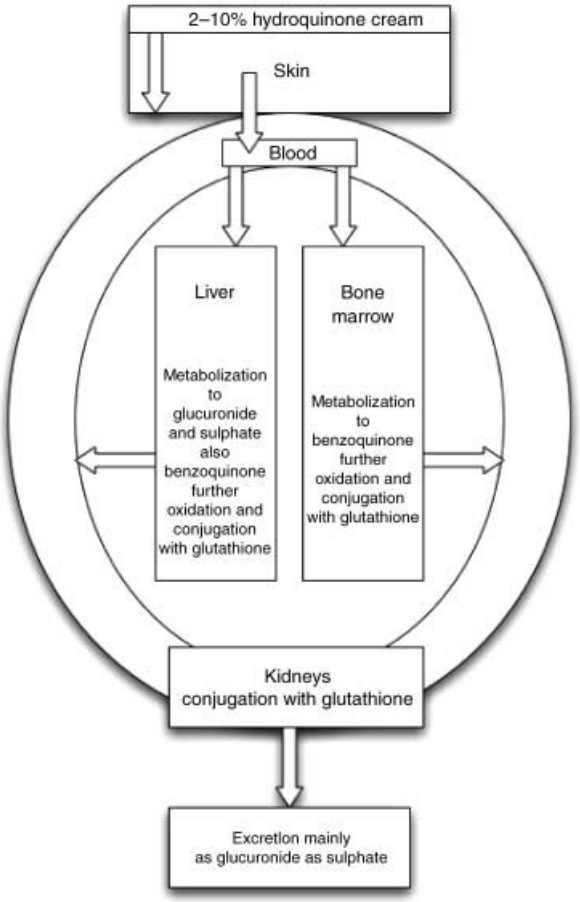

Figure 1 Schematic overview of the uptake, distribution, and metabolization of hydroquinone.

Biotransformation in liver and kidney

When hydroquinone is applied to the skin it initially circumvents the liver (the first-pass effect), so that a relatively high concentration reaches other tissues and organs, in comparison to oral ingestion of hydroquinone. The major part of hydroquinone is metabolized and detoxified via the glucuronide and sulphate route. These water-soluble metabolites are mainly excreted via the kidney.

In humans it appears that a small part of hydroquinone is not metabolized in the liver and a small part is converted into p-benzoquinone. The nonmetabolized hydroquinone and the p-benzoquinone are further conjugated with glutathione.[14,15,17] This is dependent on the activity of gamma glutamyl transpeptidase.[18] It is known that glutathione conjugates of hydroquinone, specifically 2,3,5-tris (glutathione-S-yl) hydroquinone, which impair mitochondrial function, are potent nephrotoxins.[18,19]

Metabolization in bone marrow

Because the liver is circumvented when hydroquinone is applied dermally, both the free- and protein-bound hydroquinone will penetrate the whole body, and hydroquinone will reach the bone marrow in a nonmetabolized form. The metabolism of hydroquinone in bone marrow is dependent on the peroxidase activity.

Because of the high myeloperoxidase activity and a strongly oxidative environment, the main metabolite of hydroquinone in the bone marrow is p-benzoquinone. Bone marrow is seen as the organ where long-term effects may originate.[20]

Health risk

DNA damage caused by hydroquinone

The carcinogenity of benzene is attributed to its metabolites, hydroquinone and p-benzoquinone, to covalently bond with DNA and the induction of DNA oxidation via redoxcycling, resulting in the generation of reactive oxygen species.[20]

Rao[19] described p-benzoquinone as having the ability to cause the following changes:

- single strand DNA breaks *in vitro*[21]
- suppression of granulocyte/monocyte colony formation[22]
- formation of DNA adducts
- inhibition of DNA / RNA synthesis
- inhibition of microtubular polymerization
- mitogen stimulation and inhibition of lymphocyte growth

Stillman *et al.*[23] found that hydroquinone can cause genetic 5q31 and 7 changes in human.

$CD34^{+}$ $CD19^{-}$ bone narrow cells. These cells are associated with early stages of sAML (secondary acute myeloid leukemia).

Glutathione-*S*-transferase Ml (GSTMl) is involved in the metabolic fate of hydroquinone, and polymorphisms in GSTMl could be related to interindividual differences in DNA damage arising from the exposure to this compound.[24] The ability of hydroquinone to induce a program of differentiation in the myeloblast that proceeds only to the myelocyte stage coupled with its ability to inhibit the CPP32 protease and, thereby, apoptosis of the proliferating myelocytes, may have important implications for benzene-induced acute myeloid leukemia.[25]

Influence on protective mechanisms

The previous paragraph explains that the various metabolites of hydroquinone could be involved in the induction of mutation. In general, it is the case that a genotoxic carcinogen can change the genetic information in a cell in such a way that this all escapes the regulation of cell division, which will become more or less autonomous. Although there is a seemingly complex mechanism in the development of cancer, studies show that cancer development could be the result of only a few changes in the genome. Hahn and Weinberg[26] state that as little as four to six mutations in humans are sufficient for the induction of cancer. They also state that immortality of cells is a prerequisite for the formation of tumor cells. Human cells must therefore overcome two barriers that normally determine the life span of the cell:

- replicative aging
- cellular crisis

These barriers are regulated by telomere shortening and by the RB and p53 tumor suppression route. The p53 route is significant for the development of leukemia.[26] It appears that hydroquinone and its metabolites have an influence on the overexpression of Bcl2, which plays an important role in the p53 route. Bcl2 blocks the activity of Bax which plays an important role in apoptosis[27] (Figure 2). As a result of an increased Bcl2 protein mutagenesis and carcinogenesis are enhanced by the weakening of DNA repair mechanisms and inhibition of the apoptosis of mutated cells.

Discussion

Dermatologists, general practitioners, and plastic surgeons have overlooked the large body of evidence about the long-term effects of hydroquinone leading to carcinogenesis.

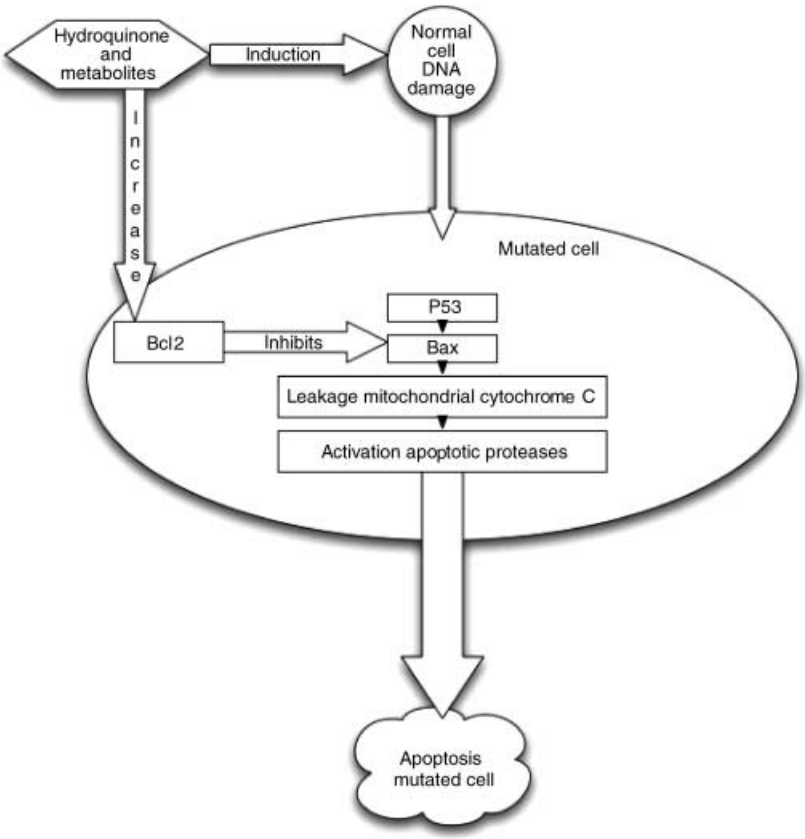

Figure 2 Schematic overview of the influence of hydroquinone and its metabolites on the development of cancer.

This is risky as they may be held responsible in the future for having prescribed topical applications containing hydroquinone. Whereas much attention has been paid to the possible hazards of hydroquinone in the work situation, where the route of entrance is mostly via the lungs, and painstaking measures were taken to lower the risk of exposure in industrial sections, hydroquinone as a cosmetic is still freely obtainable in large parts of the world, despite the fact that it was banned in many countries. As a prescription formulation for skin lightening, there are no regulations as to maximum allowable dosages.

When dermally applied, hydroquinone is rapidly absorbed by blood and is excreted slowly. The liver is partially circumvented, therefore less detoxification takes place, and more will be metabolized in other organs, particularly the bone marrow.

When hydroquinone is applied for a longer period of time, higher concentrations in the body can build up, resulting in more carcinogenous metabolites.

Currently, the long-term effects of hydroquinone such as nephrotoxicity and carcinogenity have only been demonstrated in animal experiments.[6–8] Benzene-induced leukemia develops in the bone marrow.[28] Its metabolites phenol and hydroquinone have been strongly implicated in producing leukemia associated with benzene exposure, because they reproduce the hematotoxicity of benzene, cause DNA and chromosomal damage found in leukemia, inhibit topo-isomerase II, and alter hematopoiesis and clonal selection. Additionally, hydroquinone is related to the inhibition of the apoptosis of neoplastic cells. The widely varying background levels of phenol and hydroquinone in control individuals stem mainly from direct dietary ingestion, catabolism of tyrosine and other substrates by gut bacteria, ingestion of arbutin-containing foods, cigarette smoking, and the use of some over-the-counter medicines. It is hypothesized that these background sources of phenol and hydroquinone and associated adducts play a causal role in producing some forms of de novo leukemia in the general population.[29]

It is not proven yet that hydroquinone, when dermally applied as a skin lightening agent, could lead to long-term effects such as cancer. This does not mean it that this does not take place.

This phenomenon has not been studied yet. Carefully devised epidemiologic studies are required to relate the use of hydroquinone to leukemia and the cause of death.

The long-term risks of skin malignancy from topical hydroquinone should no longer be ignored. All recent evidence from the literature indicates that the use of hydroquinone as a skin lightening agent should be stopped completely.

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