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Risk assessment of skin lightening cosmetics containing hydroquinone

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ABSTRACT

Following reports on potential risks of hydroquinone (HQ), HQ for skin lightening has been banned or restricted in Europe and the US. In contrast, HQ is not listed as a prohibited or limited ingredient for cosmetic use in Japan, and many HQ cosmetics are sold without restriction. To assess the risk of systemic effects of HQ, we examined the rat skin permeation rates of four HQ (0.3%, 1.0%, 2.6%, and 3.3%) cosmetics. The permeation coefficients ranged from 1.2×10^{-9} to 3.1×10^{-7} cm/s, with the highest value superior than the HQ aqueous solution (1.6×10^{-7} cm/s). After dermal application of the HQ cosmetics to rats, HQ in plasma was detected only in the treatment by highest coefficient cosmetic. Absorbed HQ levels treated with this highest coefficient cosmetic in humans were estimated by numerical methods, and we calculated the margin of exposure (MOE) for the estimated dose (0.017 mg/kg-bw/day in proper use) to a benchmark dose for rat renal tubule adenomas. The MOE of 559 is judged to be in a range safe for the consumer. However, further consideration may be required for regulation of cosmetic ingredients.
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1. Introduction

Hydroquinone (HQ) is used in skin bleaching agents, hair dyes, and finger nail treatments (FDA, 2009). The WHO reported that a 1% HQ aqueous solution or a 5% HQ cream caused dermal irritation in humans (WHO, 1996). Prolonged use of HQ products (1–2%) is associated with exogenous ochronosis (Findlay et al., 1975), and a worldwide total of 789 cases of exogenous ochronosis had been reported by 2007 (Levitt, 2007). In addition to these topical local effects, concerns have been raised regarding the carcinogenic potential of HQ due to its carcinogenicity concerns reported by animal studies (NTP, 1989; Shibata et al., 1991). Therefore, cosmetic use of HQ for skin lightening has been banned in the UK and EU (EC, 2009). In the US, only prescription skin lightening products can contain from greater than 2–4% HQ, and 2% or less is allowed for cosmetic use (FDA, 2009). Recently, the US Cosmetic Ingredient Review (CIR, 2014) concluded that HQ is safe at concentrations less than 1% in cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. On the other hand, HQ is not listed as a prohibited or limited ingredient for cosmetic use in Japan (MHW Japan, 2000), and many kinds of skin lightening cosmetics containing HQ are sold in Japan, some of which contain up to 10% HQ. Therefore, further information is required to evaluate whether the current use of HQ cosmetics needs to be reconsidered in Japan.

Dermal absorption of HQ was previously studied in 14 humans, and HQ was dermally absorbed in humans with a bioavailability of 45.3 ± 11.2% for a 24-h application (Wester et al., 1998). The blood elimination half-lives of HQ in a male volunteer was reported to be 16.6 min for oral administration (NDMA, 1994), and that for rats was 18.7 min for i.v. administration (Fox et al., 1986). Barber et al. (1995) indicated that permeation of HQ in the human stratum corneum was slower than that in fully thick rat skins. The permeability constant (K) values of ^{14}C-HQ solution were estimated to be 2.6×10^{-9} cm/s for human skin and 6.3×10^{-9} cm/s for rat skin (Barber et al., 1995). Bucks et al. (1988) showed that penetration of

Abbreviations: HQ, hydroquinone; i.v., intravenous; LOAEL, lowest observed adverse effect level; AUC, area under curve; BMD, benchmark dose; BMDL, lower confidence limit BMD; MOE, margin of exposure; POD, point of departure.

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HQ was reduced in presence of a sunscreen and increased with a penetration enhancer in humans (Bucks et al., 1988). Dermal absorption of HQ from cosmetics can vary among products because the absorption rate varies depending on the base formulations (Ratna, 2004). In this study, we examined rat skin permeation rates for four commercially available HQ cosmetic products (HQ-1, HQ-2, HQ-3, and HQ-4) using a side-by-side diffusion cell system to predict plasma HQ concentrations in humans after dermal absorption.

Because HQ is dermally absorbed, risk assessment for systemic effects, such as general repeated toxicity, carcinogenicity, and reproductive/developmental toxicity of HQ are required. HQ induced sister chromatid exchanged, chromosome aberrations, and/or gene mutation *in vitro* (Galloway et al., 1987; Tsutsui et al., 1997). Mutagenic carcinogens are generally considered to have irreversible effects. If HQ carcinogenesis is related to mutagenic events, the no-threshold concept should be applied for risk assessment. A transgenic mouse mutation assay in the target organs of carcinogenicity is useful to find if carcinogenesis is related to mutagenic events. We recently reported that HQ is not mutagenic in transgenic Muta™ mice (Matsumoto et al., 2014), suggesting that the mutagenic mechanism is not responsible for HQ induced carcinogenesis. McGregor (2007) also suggested that the renal tumors are exacerbated non-genotoxic spontaneous rodent renal disease that has no relevance to humans. In this study, we estimate human absorbed levels of HQ after dermal application of the HQ cosmetic with the highest permeation rate. Using the estimated human absorbed levels and toxicological data of laboratory animals in the literature, a margin of exposure (MOE) was calculated. In this paper, a risk assessment was conducted for the current use of HQ cosmetics.

2. Materials and methods

2.1. Chemicals

Four commercially available cosmetics (HQ-1, HQ-2, HQ-3, and HQ4) from different manufacturers with different concentrations of HQ (unknown concentration, 3%, 10%, and 1%, respectively) were purchased. The measured HQ concentrations in the products (HQ-1, HQ-2, HQ-3, and HQ-4) were 1.0%, 3.3%, 2.6%, and 0.3%, respectively. From our survey, 10% HQ was the highest concentration available in the market. Special grade HQ (CAS: 123-31-9; >99.0%) was purchased from Wako Pure Chemical Industries, Ltd.

2.2. In vivo studies

2.2.1. Animals

Male hairless rats (WBN/ILA-Ht; eight weeks old) were purchased from Life Science Research Center, Josai University. This species was chosen because of its wide use in toxicity and toxicokinetic studies and most commonly used for *in vivo* permeation studies. Rats were reared on a basal diet (oriental yeast) and water *ad libitum*. Animals were treated according to the ethical committee guidelines of Josai University. Hair on the abdomen was shaved about 30 min after anesthesia of sodium pentobarbital (50.0 mg/kg bw, intraperitoneal). After 12 h of fasting, *in vivo* examination of rats was conducted. During the examination, body temperature of the rats was kept using an electrical carpet.

2.2.2. Blood concentration of HQ by dermal application of HQ aqueous solution or HQ products

The male hairless rats described in 2.2.1 were used. A diffusion cell (effective surface area: 1.77 cm^2) was glued with a biological glue (Aron Alpha) on the abdominal intact skins, and 1 mL of 2% HQ aqueous solution (vehicle: saline) was applied. Stripped skins were prepared by repeating the stripping 20 times using adhesive tape (Nichiban Co., Ltd.). HQ aqueous solution was applied in the same manner as the intact skins. HQ products (HQ-1, HQ-2, HQ-3, and HQ-4) were also applied to the stripped skins as follows: The HQ products (about 100 mg) were applied on the skins, and diffusion cells filled with the HQ products were applied on the skins. The blood samples (0.2 mL) were taken from the cervical vein at 0, 30, 60, 120, 180, and 240 min after application.

2.2.3. Blood concentration of HQ by intravenous administration

Three rats were intraperitoneally anesthetized with urethane at 1.0 mg/kg. HQ aqueous solution at 2% (10 mg/kg) was administrated intravenously (i.v.), and blood samples (0.2 mL) were taken at 0, 15, 30, 60, 90, and 180 min after administration. The blood samples were centrifuged (15,000 rpm, 4 °C, 5 min), and each 0.1 mL of blood plasma was collected into a 1.5 mL microtube and kept in a freezer at −30 °C.

2.2.4. Preparation of HQ cosmetics for UPLC

Each 50 μL of HQ cosmetics was taken into a microtube, and the weight of the cosmetics was precisely measured. The sample was completely dissolved in tetrahydrofuran (4.5 times in weight) with vigorous mixing. After adding water (4.5 times in weight), the mixture was sonicated for 5 min and centrifuged. The lower layer of supernatant was taken and precisely diluted 10 times with water.

2.2.5. Determination of HQ concentration

Concentrations of HQ were determined by UPLC (ACQUITY UPLC system H-CLASS; Waters Company) equipped with a photodiode array detector (PDA eλ detector; Waters Company). Limit of detection (LOD) of HQ was determined as signal-to-noise ratio of 3 and was 0.06 mg/mL. An ACQUITY BEH C18 column (size: 2.1 mm i.d. × 50 mm; particle size: 1.7 μm; Waters Company) was used at 40 °C. Five microliter of test solution was injected. Acetonitrile (5% or 10%) was used as a mobile phase and a flow rate was set to 0.1 mL/min. The scanning range of wavelength was set to 210–400 nm. HQ was detected and quantitated at 288–289 nm. The absolute calibration curve method was used for measurement of HQ. Water solution containing special grade HQ was used as a standard solution.

2.3. In vitro studies

2.3.1. Determination of HQ concentration for release and permeation studies

HQ release and skin permeation from the studied products were examined by a side-by-side diffusion cell system. For the release study, a cellulose dialysis membrane (UC24-32-100, EIDIA Co., Ltd., Tokyo, Japan) was placed in between the diffusion cells. The cellulose dialysis membrane was chosen because it is widely used for drug release studies. For the permeation study, abdominal skin pieces were excised from rats under anesthesia of sodium pentobarbital (50.0 mg/kg bw, intraperitoneal) and one piece of intact skin was set in between the diffusion cells (effective surface area: 0.95 cm^2). The intact rat skin data were used for a realistic exposure assessment because HQ-containing products are generally applied to intact human skin. Full-thickness skins were used as defined by OECD TG 428 in this study (OECD, 2004). Permeability of hydrophilic chemicals like HQ would not be affected by skin thickness in contrast to lipophilic chemicals (Yamaguchi et al., 2008). The thickness of the skin was measured according to a method reported previously (Watanabe, 2001). The biotransformation was not inhibited in this system. Each HQ product (HQ-1, HQ-2, HQ-3, or HQ-4 at 250 mg) was applied on one side of the cellulose

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