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Human stratum corneum penetration by copper: In vivo study after occlusive and semi-occlusive application of the metal as powder

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Abstract

Aim of the study was to shed light on the long-standing controversy whether wearing copper bangles benefits patients suffering from inflammatory conditions such as arthritis.

Sequential tape stripping was implemented on healthy volunteers to examine the diffusion of copper through human stratum corneum in vivo following application of the metal as powder on the volar forearm for periods of up to 72 h.

Exposure sites were stripped 20 times and the strips analyzed for metal content by inductively coupled plasma-mass spectroscopy with a detection limit for copper of 0.5 ppb.

Untreated skin was stripped in the same fashion, to determine baseline copper levels for comparison with exposure values resulting from exposure in respective volunteers.

Under occlusion with exclusion of air, up to 72 h copper values decreased from the superficial to the deeper layers of the stratum corneum with gradients increasing commensurately with occlusion time, characteristic of passive diffusion processes. From the tenth strip on, however, levels reverted to background values.

Under semi-occlusion allowing access of air by covering the skin with "breathable" tape, initial copper values lay significantly above baseline values and concentration gradients increased proportionally with occlusion time. At 72 h, from the tenth to the twentieth strip reaching the glistening epidermal layer, copper values continued at constant levels, significantly above baseline values.

The results indicate that, in contact with skin, copper will oxidize and may penetrate the stratum corneum after forming an ion pair with skin exudates. The rate of reaction seems to depend on contact time and availability of oxygen. A marked inter-individual difference was observed in baseline values and amounts copper absorbed.
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1. Introduction

Arthritis patients have worn copper jewelry of various types for thousands of years for the relief of inflammation and musculoskeletal disorders. Their use continues today as folk remedy. Data documenting statistically significant amelioration of arthritic conditions in patients wearing copper objects in intimate contact with skin as compared with the effect of placebo objects, however, are missing to date.

Indicative of the process of skin penetration by certain metals is the short term onset of skin reactions, primarily

Abbreviations: AI, anti-inflammatory; AUC, area-under-the-curve; eV, electron Volt; SC, stratum corneum; sc, sub cutaneous; ICP-MS, Inductively coupled plasma-mass spectroscopy.

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immunologic or non-immunologic irritation, resulting from contact with coinage, tools, jewelry or other articles of daily use. Major skin reactions to metals involve nickel (Lidén and Carter, 2001) and chromium (Wass and Wahlberg, 1991). Few reports suggest skin reactions to copper also (Black, 1972; Karlberg et al., 1983; Saltzer and Wilson, 1968; Fat and Gyorffy, 2005).

It remains to be demonstrated that copper metal in contact with the skin does diffuse through the SC to reach the nucleated epidermis, becoming locally or systemically available. The critical factor in determining if a metal will penetrate the SC is believed to be the formation of soluble compounds. Skin exudates may lead to electrochemical reactions resulting in metal oxidation (corrosion) to form potentially skin-diffusible compounds with naturally present, skin-identical anions such as chloride ion, with amino acids or with fatty acids present on the skin surface (Hostýnek, 2003a; Hostýnek, 2003b). Such reactions usually become apparent through the discoloration of the skin in the areas of contact.

So far, this phenomenon of copper metal dissolution in (artificial) sweat in vitro, its uptake into the SC and its clinical effects has been supported by a number of investigations. After immersion of copper turnings in human sweat over 24 h, the metal concentration increased by an average of 2 orders of magnitude from the natural level: from 1–3.5×10^{-5} M to 0.6–3.4×10^{-3} M (Walker and Griffin, 1976). In animals, copper complexes generated on sustained contact of the metal with the skin appeared to exert AI activity; that was attributed to the action of copper compounds formed in situ and their cutaneous absorption (Whitehouse et al., 1977). A strong argument in favor of the therapeutic activity of elemental copper brought in intimate contact with the organism was provided earlier in an animal study which demonstrated the anti inflammatory (AI) properties of copper metal present in the organism: a clear prophylactic effect was achieved when experimental inflammation failed to be induced in rats in which copper metal had been implanted two months prior to the experiment (Dollwet et al., 1981).

It remains to be demonstrated that copper penetrates the skin upon exposure to the metal in vivo, and thus potential AI effects could be achieved by dermal exposure in humans also. In order to arrive at a conclusive assessment of skin penetration by copper, evidence of cutaneous penetration on contact may be obtained by use of quantitative metal analysis of superficial epidermal strata.

The purpose of the present investigation into the fate of metallic copper brought in intimate contact with the skin was (I) to obtain (semi-quantitative) evidence for the formation of copper complexes which diffuse and are detectable by the presence of copper in the SC, (II) to trace the kinetics of copper diffusion through the SC, (III) to assess adsorption and reservoir formation by the penetrating metal in the SC, and (IV) determine whether copper absorbed over time could penetrate beyond the SC and become available for systemic absorption. Credence could thus be conferred to the contended benefits of relief from musculoskeletal disorders attributed to the wearing of copper jewelry, as the potential for the metal's activity as an AI agent by dermal exposure in its elemental state is still subject to controversy.

Determining kinetics and penetration depth of permeants by tracing the concentration profiles in SC has been rendered facile by using the virtually non-invasive method of SC stripping with adhesive tape (Bommannan et al., 1990; Cullander et al., 2000; Higo et al., 1993; Loeffler et al., 2004; Rougier et al., 1987; van der Molen et al., 1997) and the detection of minute quantities of metals using ICP-MS analysis. It is now possible to analyze for the presence of elements such as copper in skin and other biological materials, with detection limits on the order of 0.5 ppb (Parsons et al., 1983), making the use of radioisotopes unnecessary.

2. Experimental

2.1. Subjects

Healthy Caucasian volunteers between the ages of 34 and 69 without evident dermatological disease participated after giving informed consent. The study was approved by the University of California Committee on Human Research. The volar forearm was selected as study site. Three replicates on adjacent sites were conducted on the same volunteer.

2.2. Copper application, occlusion, decontamination and stripping

For the purpose of determining baseline copper values, the naturally occurring copper in the skin of the volunteers was first determined by analyzing three sequential strips from three untreated sites on the volar forearm of each volunteer. This was followed by copper application with 3 iterations for each occlusion period, on the volar forearm of the participating volunteers. For occlusion of the SC, plastic chambers of 12 mm diameter (1.15 cm^2) were placed on the pre-marked area of the flexor surface on the arm, the chamber covered with the dressing and left for the predetermined length of time (24, 48 and 72 h). The occlusive and semi-occlusive application systems consisted of a plastic chamber (Hill-Top Res., Inc., Cincinnati, USA) and Micropore semi-occlusive tape (3M Health Care, St. Paul, MN, USA), respectively.

Copper powder (99.7% 3 mm particle size (Aldrich Chem. Co., Milwaukee, WI)) was applied in triplicate on 3 volunteers. Prior to application, skin sites were cleansed with deionized water and dried using cotton swabs. Copper powder was applied on the volar forearm between wrist and antecubital fossa. The experiment was conducted during the months of September through April, whereby the exposed skin of the volunteers exhibited no noticeable tanning. Copper powder (25 mg) was placed on a plastic chamber, the chamber then placed on the pre-marked area of the flexor

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