

A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals

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Chelating agents in protective barrier creams have often been used in the prevention of allergic contact dermatitis to nickel. In a pilot study, we demonstrated the preventive effect of 10% diethylenetriaminepentaacetic acid (DTPA) in an oil-in-water emulsion in nickel-sensitized patients. Now we reproduced these results in a randomized, double-blind study. Additionally, we investigated the efficacy of the barrier cream in other clinically relevant metal allergies. Individuals sensitized to various metals had a significant decrease in positive patch test reactions after pre-treatment with the DTPA-cream: 2.5% nickel sulfate (24/28 positive without pre-treatment versus 1/28 with pre-treatment; $p < 0.0001$), 5% nickel sulfate (30/32 versus 15/32; $p = 0.0003$), 1% cobalt chloride (19/20 versus 6/20; $p = 0.001$) and 5% copper sulfate (13/14 versus 5/14; $p = 0.02$). However, the cream had no protective effect with 1% palladium chloride (17/23 versus 16/23) and with 0.5% potassium dichromate (9/13 versus 7/13). We conclude that the DTPA-cream clearly abrogates positive patch test reactions in nickel-, cobalt- and copper-sensitized subjects and that it may therefore be helpful in the management of allergic contact dermatitis.

Key words: contact dermatitis; metal allergy; metal hypersensitivity; nickel; cobalt; copper; barrier cream; chelating agents; DTPA; skin care products; prevention. © Munksgaard, 2001.

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Allergic contact dermatitis (ACD) caused by metals is a common problem. Usually these metals are not a major part of consumer products but minor compounds of metal alloys or low level impurities of the raw materials (1, 2). The clinically most relevant metal allergen is nickel. Nevertheless, chromium, cobalt, palladium and copper are clinically relevant allergens as well. Jewellery and personal metal objects like wristwatches and jeans buttons have been identified as the most important sources of nickel as well as cobalt (1). Chromium allergy is a common cause of occupational disease, e.g., in cement workers (1). Palladium is commonly used in dental alloys and jewellery (3). Copper is reported as a rare allergen (4). However, we have often observed positive patch tests to copper in our

clinic (unpublished results). Therefore we included copper in our study as well. Additionally, most of these metals are widely used in dentistry. Vilaplana et al. (5) report that various dental alloys can contain 1 or more of the above-mentioned metals.

The best way to prevent the flare-up of ACD in a sensitized individual is by avoiding direct skin contact with the relevant allergen. However, particularly occupational exposure often does not permit this ideal condition. Gloves or barrier creams applied before exposure are usually proposed as alternative solutions (6).

Creams are of great importance in the prevention and treatment of contact dermatitis, especially on the hands. An optimal barrier cream should be able to block completely contact between the allergen and the skin like a glove (7). Though many preparations have so far been tested, none has shown sufficient potential for practical use (8–11). Agents like ion exchangers have been added to creams to increase their protective efficacy (12, 13). Chelating agents such as ethylenediaminetetra-

Abbreviations:

ACD: allergic contact dermatitis; DTPA: diethylenetriaminepentaacetic acid; EDTA: ethylenediaminetetraacetic acid; HY: hydrocream; HY-DTPA: 10% diethylenetriaminepentaacetic acid in hydrocream; ICDRG: International Contact Dermatitis Research Group; $\log K_1$: stability constant.

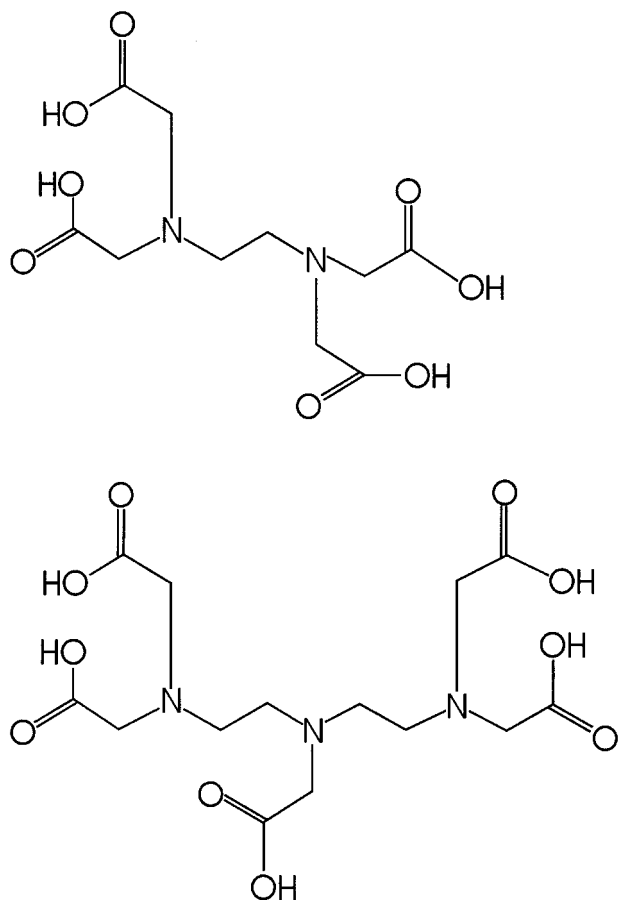


Fig. 1. Comparison of the molecular structure of DTPA (bottom) and EDTA (top).

acetic acid (EDTA; Fig. 1) complex the metal ion and can conceal it from the immune system. Their addition increases the efficacy of creams (14; reviewed by Gawkrödger et al. (15)). Fullerton & Menné (16) showed that a gel containing the chelator EDTA can immobilize nickel ions and reduce their penetration into the epidermis. Clioquinol gave the best results in preventing nickel dermatitis (17). However, its use is limited because it is an allergen in its own right (18, 19).

Diethylenetriaminepentaacetic acid (DTPA; Fig. 1) is structurally similar to EDTA. Systemically administered DTPA has successfully been used for detoxification of the bivalent metal ion cadmium (20, 21). Resl et al. (22) found that DTPA has a more pronounced detoxifying capacity for chromium, nickel and cobalt than EDTA. They also found that it was well tolerated on the skin. Nonetheless, DTPA had never been used in the context of barrier creams. In a pilot study (23) we evaluated the capability of various barrier creams in preventing skin reactions in nickel-sensitive individuals. 4 chelating compounds in 2 different vehicles were tested. The combination of 10% DTPA

in an oil-in-water emulsion (35% lipids/64% water) showed the most promising results.

In this work, we re-evaluated the skin-protective capacities of the DTPA-containing protection cream in a randomized and double-blind study. We also extended the range of metal allergens examined from nickel to the less frequent metal allergens cobalt, copper, palladium, and chromium.

Patients and Methods

Patients

Over a period of 1 year, 45 subjects (41 female / 4 male, mean age 34 years, range 14 to 56) with positive patch tests to nickel, cobalt, copper, palladium and/or chromium were enrolled in the study. We specifically selected patients with rare metal sensitivities. Most of the patients were sensitized to more than 1 metal allergen (Table 1).

Vehicle and Chelator

Diethylenetriaminepentaacetic acid (DTPA, CaNa_3 salt, SIGMA) was used at a concentration of 10% in an oil-in-water emulsion (hydrocream HY/Excipial Hydrocreme®, Spirig, Switzerland; 35% lipids/64% water).

Clinical testing

All patients were re-tested to the following metals: nickel sulfate (NiSO_4 2.5% and 5% pet.), palladium chloride (PdCl_2 1% pet.), cobalt chloride (CoCl_2 1% pet.), potassium dichromate ($\text{Cr}_2\text{K}_2\text{O}_7$ 0.5% pet.) and copper sulfate (CuSO_4 5% pet.). All

Table 1. Summary of all observed patch test reactions; the total number of 45 patients was recruited to 1 or more subgroups depending on their respective sensitization; HY vehicle, HY-DTPA vehicle+active agent

	+++	++	+	Negative	Total
Ni 5%	16	9	5	2	32
Ni 5%+HY	14	9	5	4	32
Ni 5%+HY-DTPA	1	9	5	17	32
Ni 2.5%	8	8	8	4	28
Ni 2.5%+HY	11	6	8	3	28
Ni 2.5%+HY-DTPA	1	0	0	27	28
Co	6	6	7	1	20
Co+HY-DTPA	0	2	4	14	20
Cu	1	3	9	1	14
Cu+HY-DTPA	0	1	4	9	14
Pd	2	3	12	6	23
Pd+HY-DTPA	4	5	7	7	23
Cr	1	3	5	4	13
Cr+HY-DTPA	2	1	4	6	13

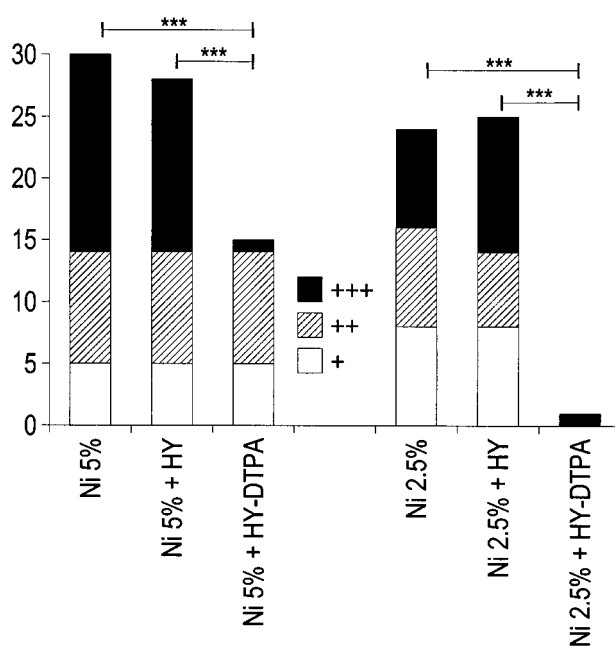


Fig. 2. DTPA-HY prevents positive patch tests with 5% nickel ($***p < 0.0005$) as well as with 2.5% nickel ($***p < 0.0001$), while HY alone has no protective effect. DTPA-HY also reduces the severity of the observed patch test reactions with 5% nickel and 2.5% nickel, while again HY had no protective effect ($***p < 0.0001$ in all cases). The sign test was used to judge whether the occurrence of an allergic skin reaction was prevented with the DTPA-containing vehicle. The Wilcoxon signed rank test was employed to ask whether the severity of the ACD could be reduced. The y-axis depicts the number of positive patch test results.

these substances were bought from Brial, Germany.

2 identical blocks consisting of 8 circular areas of 3 cm² each were tested on the left and right outer upper arms. The samples were randomized and applied in the following manner: each of the 6 tested substances was tested on a non pre-treated patch and on a patch pre-treated with 0.02 ml of the DTPA-containing vehicle. 2 patches were pre-treated with the vehicle alone and exposed to 2.5% and 5% NiSO₄, respectively. On the remaining 2 fields the vehicle and the vehicle with DTPA were tested as negative controls. The pre-treated areas were let dry for 10 min, before single patches using the Cura test system (Lohmann GmbH & Co KG, Germany) were applied. The reading was done after 3 days by a 3rd party following the ICDRG criteria.

Statistical analysis

All patients showing any positive skin reactions upon re-testing (either to allergen and/or allergen+HY and/or allergen+HY-DTPA) were considered for the statistical analysis (Table 1).

The sign test was used to judge whether the occurrence of an allergic skin reaction was prevented with the DTPA-containing vehicle. The Wilcoxon signed rank test was employed to ask whether the severity of the ACD could be reduced.

Results

DTPA-HY reduces the number of positive patch test reactions to nickel sulfate. DTPA is the active component of DTPA-HY (Fig. 2, Table 1)

Pre-treating the skin with DTPA-HY reduced the clinical reaction to 2.5% nickel in a highly significant way, showing positive skin reactions in only 1 out of 28 persons. DTPA is the active agent in DTPA-HY because HY alone was not able to protect the skin in comparison with the nickel positive control (24 v 25 positive skin reactions out of 28).

Doubling the concentration of nickel to 5% reduced the protective effect while still being statistically highly significant. DTPA-HY pre-treatment prevented positive tests in 17/32 subjects. Again HY alone had no protective effect as 28 out of 32 persons had a positive skin reaction v 30 with nickel alone (positive control).

In those individuals still showing positive skin reactions DTPA-HY can decrease the severity of the patch test reactions (Fig. 2, Table 1)

Focusing on the severity of the allergic reaction, the number of +++ reactions decreased from 8 to 1 when using 2.5% nickel. The reduction was even more pronounced with 5% nickel: 16 +++ reactions versus 1 +++ reaction following DTPA-HY pre-treatment. With both concentrations of nickel this was a highly significant result.

DTPA-HY reduces allergic skin reactions also to cobalt (Co) and copper (Cu) but not to chromium (Cr) and palladium (Pd) (Fig. 3, Table 1)

20 individuals qualified as being sensitized to cobalt. Of 19 individuals with a positive patch test to 1% cobalt, 14 showed no signs of allergic reaction after pre-treatment with DTPA-HY. This was a highly significant reduction. Additionally DTPA-HY decreased the severity of the skin reaction in a highly significant way. No +++ reactions were seen on the pre-treated sites in comparison with 6 +++ on the positive controls.

As copper is a rare allergen only 14 individuals could be recruited to this sub-group. 13 out of 14 patients had a positive patch test to copper. Pre-treatment with DTPA-HY significantly decreased the number to 5 positive patch test results. Also

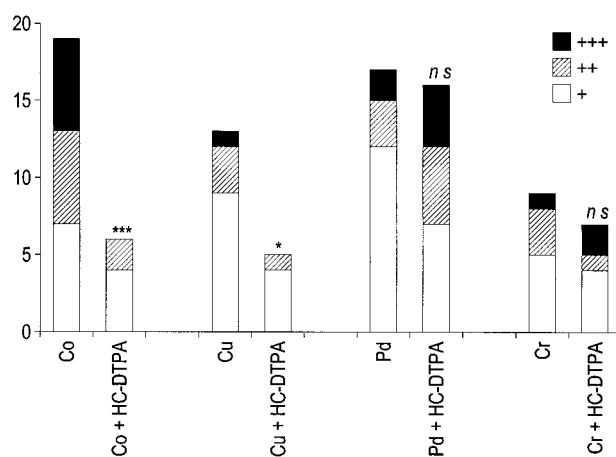


Fig. 3. DTPA-HY prevents positive patch tests in individuals sensitive to cobalt ($***p=0.001$) and copper ($*p=0.02$). The severity of the reactions is also reduced: cobalt ($***p<0.0001$), copper ($*p=0.02$). No significant (ns) effects were observed in palladium- and chromium-sensitive subjects. The sign test was used to judge whether the occurrence of an allergic skin reaction was prevented with the DTPA-containing vehicle. The Wilcoxon signed rank test was employed to ask whether the severity of the ACD could be reduced. The y-axis depicts the number of positive patch test results.

the severity of the patch test reactions was reduced significantly.

No effect was detected in the context of palladium hypersensitivity. 7 of 23 pre-treated sites gave no positive test result in comparison with 6 in the positive controls.

DTPA-HY had no significant protecting effect in the context of chromium sensitization. 6 out of 13 subjects with pre-treatment and 4 without pre-treatment remained without a positive patch test reaction.

Negative controls produced no skin irritation

HY alone and HY-DTPA (negative controls) did not provoke skin irritation in any case.

Discussion

This study showed that diethylenetriaminepentaacetic acid/hydrocream (HY-DTPA) is an effective protective barrier cream in metal-sensitive subjects. The application of HY-DTPA effectively protected from positive patch test reactions to nickel. This confirmed the results of our pilot study (23). HY-DTPA more efficiently protects from 2.5% nickel-sulfate than from 5%. We explain this observation with an excess of free nickel ions in comparison with the DTPA-molecules in the cream. Therefore a considerable amount of nickel ions remains in an unbound form. In daily life nickel-sensitive pa-

tients usually never face exposure to nickel in concentrations so high. Hence this does not limit the practical use of HY-DTPA.

DTPA is known to form stable complexes with the other tested metals too. Therefore we had speculated that DTPA could also help in the context of other metal allergies. This turned out to be true for cobalt and copper but not for palladium and chromium. Differences in the stability constants $\log K_1$ for the relevant metal-DTPA salts cannot explain these results, as $\log K_1$ for Co(II)DTPA is the lowest with 18.4 whereas Pd(II)DTPA has the highest $\log K_1$ with 24.6. At the molar level palladium was tested at a comparable concentration of around 3.4 to 4 mM to nickel and cobalt. Still, DTPA-HY can only give protection to nickel-, cobalt- and copper-sensitized individuals.

Nickel, palladium, cobalt and copper are allergenic as bivalent metal cations (2). Chromium is the only trivalent ion among the tested metal allergens. This and the lower $\log K_1$ for Cr(III)DTPA with 15.36 might explain why DTPA-HY cannot avert dermatitis in chromium-sensitized subjects. The reason why DTPA-HY has no effect on the prevention of palladium dermatitis remains unclear.

Perhaps the combination of the vehicle and the active compound play an important role in the efficacy of the barrier cream. We addressed this question in the context of nickel-hypersensitivity in our pilot study (23). Therein we compared different combinations of the oil-in-water emulsion HY and a water-in-oil emulsion (lipocream LC/Excipient Lipocreme®, Spirig AG, Switzerland; 54% lipids/43% water) with the chelating agents DTPA, ethylenediaminepentaacetic acid (EDTA; Fig. 1), phenanthroline and mannitol for their ability to protect from allergic contact dermatitis in nickel-sensitive subjects. Both combinations, 10% DTPA in HY and 10% EDTA in HY, showed good results. However, the DTPA-HY formula was chosen as the best due to its higher galenic stability in comparison to the EDTA-HY formula.

Berndt et al. (24) showed that the vehicle of a barrier cream alone can have a positive effect on the skin's status. We demonstrated that pure HY could neither block nor reduce the severity of the nickel dermatitis reaction in sensitized individuals. This indicates that DTPA is the active component in HY-DTPA. It is quite reasonable to assume that this also is the case for the protective effect we observed with copper- and cobalt-sensitivity.

DTPA-HY is safe. Systemically administered DTPA has been safely used for the detoxification of heavy metals for a long time (25, 21). Adverse reactions to DTPA-HY such as skin irritation

seem to be very rare. We never encountered any of them either in our pilot study or in this one. Since the introduction of DTPA-HY in our clinic as a therapeutic option for nickel-allergic patients in 1998, we have never seen any adverse effects either.

The use of a protecting cream such as DTPA-HY prior to exposure fits into a comprehensive concept for patients sensitized to metals, who cannot thoroughly avoid allergen contact and who cannot wear protective gloves. There are further therapeutic options: Fullerton and Hoelgaard (26) showed that significant amounts of nickel remain bound to the epidermis after skin contact. Therefore it is worth washing the hands thoroughly after skin contact because considerable amounts can be washed off. This effect can be enhanced using a cleansing solution containing the chelating agent EDTA and/or histidine (27). Fullerton & Menné (16) also recommend thorough hand-washing after the use of a protecting gel, because considerable amounts of nickel ions remain on the skin in the form of complexes with the chelating agent.

We conclude that the use of DTPA-HY offers a reasonable therapeutical option to patients not only sensitized to nickel but also to cobalt or copper. However, the regular, frequent and correct application of a protective cream is still the basis for its efficacy (24).

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