Treatment of Nickel Dermatitis
(The Influence of Tetraethylthiuramdisulfide (Antabuse®) on Nickel Metabolism)

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ABSTRACT

Nickel is the most common cause of allergic contact dermatitis in females. The dermatitis can be maintained both by direct contact and by ingestion of nickel. In 9 out of 17 patients suffering from dermatitis, a diet with a low nickel content has improved their condition.

Eleven patients with chronic nickel hand dermatitis were given a daily dosage of 200 to 400 mg of tetraethylthiuramdisulfide (Antabuse®). Antabuse® is metabolized to the nickel chelating substance sodium diethyl-dithiocarbamate. In eight patients, the dermatitis cleared. Measurements of serum and urine nickel were performed in six patients. One week after the start of the Antabuse® treatment, the urine nickel rose from 1 to 3.6 µg per 24 hours to 8.3 to 76.0 µg per 24 hours. The serum nickel rose from 0.26 to 0.80 µg per l to 2.0 to 7.7 µg per l. In four patients the serum nickel exhibited a declining tendency during the treatment period. The results suggest that Antabuse® is able to reduce the nickel deposits in man.

Nickel metabolism has previously been investigated from the viewpoint of the acute toxicology of the nickel carbonyl vapours and for its carcinogenic effect. More recently, attention has been drawn to nickel metabolism in another context. Nickel has been known as a contact allergen for years. Patients sensitized to nickel often develop hand dermatitis with a chronic course.

In 1975, Christensen and Moller showed that ingestion of nickel in amounts comparable to the normal daily nickel intake led to an exacerbation of the hand dermatitis in nickel sensitive patients. Hand dermatitis is not life-threatening, but its common occurrence makes it an important problem. In Denmark, hand dermatitis from nickel allergy is the most common skin disease.
leading to permanent disability,\textsuperscript{5} and an unknown number of persons have sick leaves of long duration.

Following the observation of Christensen and Moller, the most logical treatment of long-term nickel hand dermatitis has been to prescribe a diet low in nickel or to treat the patient with a nickel chelating agent.

Improvement of the hand eczema was seen in 50 percent of a group of nickel sensitive patients when their nickel intake was decreased.\textsuperscript{4} However, the diet is difficult to maintain and is not suitable in routine clinical treatment.

Since the early 1950's, sodium diethyl-dithiocarbamate has been used in the treatment of acute nickel carbonyl poisoning.\textsuperscript{9} Two molecules of sodium diethyl-dithiocarbamate combine with the nickel ion to form a complex excreted in the urine.\textsuperscript{11} One patient with Wilson's disease, who was treated both intravenously and orally with sodium diethyl-dithiocarbamate, exhibited a negative nickel balance after four to six days of this treatment.\textsuperscript{11}

Extensive long-term experiments with sodium diethyl-dithiocarbamate in rats and dogs do not reveal any serious side effects. Especially interesting is the fact that there was no depletion of iron, calcium and manganese.\textsuperscript{12}

The literature has recently been reviewed by Sunderman.\textsuperscript{15} No deaths occurred among 350 cases of accidental nickel carbonyl poisoning treated with sodium diethyl-dithiocarbamate. As sodium diethyl-dithiocarbamate is still categorized as an experimental drug in Denmark, the present authors decided to try tetraethylthiuramdisulfide (Antabuse\textsuperscript{®}) in patients with chronic nickel dermatitis. Antabuse\textsuperscript{®} is metabolized to two molecules of sodium diethyl-dithiocarbamate.\textsuperscript{8,15} Earlier, West and Sunderman\textsuperscript{16} have shown that against the toxicity of nickel\textsuperscript{carbonyl} vapours Antabuse\textsuperscript{®} has certain protective properties, though not as effective as sodium diethyl-dithiocarbamate.

Samitz & Pomerantz\textsuperscript{7} demonstrated that nickel chelated to diethyl-dithiocarbamate is unable to provoke a dermatitis in nickel sensitive patients. As chronic nickel hand dermatitis is often maintained by oral ingestion of nickel, Antabuse\textsuperscript{®} could be a new method of treatment which might well prove effective.

**Material**

Eleven patients with long-lasting nickel hand dermatitis participated in the open study.\textsuperscript{3} Antabuse\textsuperscript{®} was administered in dosages of 200 to 400 mg a day (figure 1). The nickel concentrations in serum and urine were measured in six patients before and during the treatment. The patients kept their normal diet during the treatment.

**Method**

Blood samples were obtained using polyethylene catheters (Intracath\textsuperscript{®}) and acid washed tubes. The 24-hour urine samples were collected in acid washed plastic containers.

Five ml of urine or serum were dried and ashed in platinum or fused silica crucibles at 550°C until a white ash remained. The residue was dissolved and transferred quantitatively to a 10 ml glass stoppered test tube using a total of 5 ml of 1 molar nitric acid. The solution was buffered to pH 5 by adding 2 ml of 1.5 molar sodium-citrate and solvent extracted by adding from 0.25 to 2.0 ml xylene with 5 percent diethylammoniumdiethyl-dithiocarbamate and shaking for two minutes. The nickel analysis was performed by flameless atomic absorption spectrometry\textsuperscript{*} by injecting 50 \(\mu\)l of the xylene extract. The detection limit of this method, employing a minimum volume of

\* Perkin-Elmer, Model 370, equipped with heated graphite atomizer, HGA 76.
xylene (0.25 ml), is approximately 0.1 μg per l of nickel.

Results

The urine and serum nickel before treatment were 1 to 3.6 μg per 24 h and 0.21 to 0.80 μg per l. After the start of the Antabuse® treatment, the urine nickel rose to 8.3 to 76.0 μg per 24 h within eight days (figure 1). In patient B, the rise was gradual over a period of two weeks. Maintaining the same Antabuse® dose, the urine level showed a falling tendency during the following weeks in all patients except patient E.

The serum level rose to 2.0 to 7.7 μg per l during the first eight days and fell during the following weeks (figure 1). In patients A, B, D and E, the increase in the Antabuse® dose was followed by an increase of the urine nickel, but the serum nickel exhibited a steadily falling tendency.

Transient exacerbation of the dermatitis was seen after two to seven days of treatment in nine of the 11 patients. Dermatitis cleared in eight of the 11 patients. Among those whose urine and serum nickel were
measured, patients A, B, D and E had excellent clinical responses with a total clearing of their earlier chronic dermatitis. Patients F and C had severe exacerbation during the Antabuse® treatment, and they never cleared.

Discussion

Pre-treatment levels of nickel in urine were found comparable to those reported in other studies, while our serum values were lower. The initial rise in the urine and serum nickel after the start of the Antabuse® treatment probably reflects a mobilization of nickel from the deposits in the skin and cartilage. It cannot be due to increased nickel absorption from the intestine. The observation of an initial exacerbation of the dermatitis in eight of the 11 patients is probably due to the increased nickel level in the serum. In patients A, B, D and E, the second increase of the Antabuse® dosage from 300 to 400 mg daily was followed by an elevation of the urine nickel excretion and a trend towards declining serum nickel. This could be a sign that the nickel deposits in the body were being depleted. All four patients had an excellent clinical response to the treatment. Earlier, Sunderman found a negative balance in one female patient with Wilson’s disease treated with sodium diethyldithiocarbamate. The hand dermatitis healed in eight of 11 patients treated. The effect of this treatment supports the contention that the chronic hand dermatitis of some nickel hypersensitive patients is maintained by the ingestion of nickel.

Side effects, such as headaches and dizziness, were frequent, probably owing to the relatively high Antabuse® dosage used in this preliminary study. Later five similar patients were treated starting with a dose of 50 mg and gradually increasing it to 200 mg over a period of four weeks. With this schedule, no initial flare of the hand dermatitis was observed, and other side effects were mild. Even so, an improvement of the nickel dermatitis was achieved. To confirm the therapeutic effect of Antabuse® in patients suffering from chronic nickel hand dermatitis, a double-blind study has been started comparing Antabuse® with a placebo.

The present study confirms that Antabuse® is an effective nickel chelating agent in man. However, in the treatment of acute nickel carbonyl poisoning, sodium diethyldithiocarbamate and penicillamine are more effective than Antabuse®. If chelating agents can prevent the development of cancers in animals injected with Ni₃S₂, Antabuse® could be used in the treatment of industrial workers who have been exposed to high amounts of nickel and who, upon retirement, still have large amounts of nickel in their nose and lungs, and a high rate of nasal and lung cancer.

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References

7. Samitz, M. H. and Pomerantz, H.: Studies of


