Use of Sodium Diethyldithiocarbamate in the Treatment of Nickel Carbonyl Poisoning*

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ABSTRACT

This presentation is primarily concerned with the use of sodium diethyldithiocarbamate (Dithiocarb) in the treatment of acute nickel carbonyl poisoning. Reference will be made to earlier studies pertaining to diagnosis in relation to treatment. In addition, recent studies will be briefly considered on the administration of Dithiocarb to rats developing tumors following the muscular implantations of nickel subsulfide (Ni$_3$S$_2$).

Introduction

In 1943 during World War II, it became apparent that exposure to nickel carbonyl presented a serious health hazard and a deterrent to research in atomic energy. As a consequence, studies were initiated at that time (and have been continued to the present) to develop methods for the early detection of nickel carbonyl poisoning in persons who might have been unknowingly exposed to it and to establish therapeutic measures for its treatment.

Obviously, the simplest method of determining the presence of a noxious substance in air is its detection by odor. However, nickel carbonyl, even in hazardous concentrations, has only a mild, non-penetrating odor, often described as "sooty" or "musty." In our laboratory, an attempt was made to establish the limits in which nickel carbonyl could be detected by smell. Six laboratory workers were asked to indicate the presence of nickel carbonyl by smelling whiffs of samples of nickel carbonyl in air ranging in concentrations from 0 to 5 ppm. The results were totally erratic, and it was concluded that the presence of nickel carbonyl is likely to be undetected by those unfamiliar with it. For example, in an accident that occurred in an oil refinery 35 years ago in which more than 100 persons were exposed to nickel carbonyl, there was no suspicion of exposure until the workmen became acutely ill.

The first monitoring system which was developed in our laboratories for the detection of nickel carbonyl in air was a simple, manually operated rotameter and suction pump which permitted air to be drawn into an absorber in which nickel carbonyl vapor was converted to a nickel halide by its reaction with bromine or chlorine. The smoke formed was capable of scattering light, and the intensity of the scattered light could be related to the concentration of nickel carbonyl in the contaminated air. This device, which was called “the sniffer”, had a sensitivity of less than one ppm and was reasonably precise. The system was later modified and adapted for the

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continuous, automatic monitoring of working areas. For the past 20 or more years, the procedure was replaced by sophisticated conductimetric and chemiluminescent instrumentation.

**Diagnosis**

In our initial efforts to establish criteria for the early diagnosis of acute nickel carbonyl poisoning, it was realized that in addition to monitoring the working areas, it became essential to develop a reliable chemical method for the analysis of nickel which would not only detect trace amounts in biological fluids but would also provide an estimate of the severity of exposure. Furthermore, it was desirable that such a method be rapid, economical of material, of easy manipulation, and adaptable for routine purposes. To meet these criteria, the method of Alexander, Godar, and Linde was modified and became well adapted for the routine analysis of nickel in urine. It should be noted that this method afforded the clue which led to the investigations and discovery of sodium diethyldithiocarbamate as a specific antidote for nickel carbonyl poisoning. This chemical is the chelating color reagent used in the procedure for measuring nickel in urine. In recent years, measurements of greater accuracy and specificity by atomic absorption spectrometry have replaced the early colorimetric measurements.

In studies of nickel metabolism in dogs, it will be seen in figure 1 that after exposure to nickel carbonyl more than twice as much nickel was excreted in the urine as in the feces. The observation that there is a sharp increase in nickel excretion in urine immediately after exposure to nickel carbonyl proved to be of major practical importance. It enabled the detection of exposure in workers to minimal amounts of nickel carbonyl frequently before the onset of symptoms. Furthermore, measurement of the nickel concentration in urine collected after exposure proved to be a valuable aid in classifying patients as a guide to Dithiocarb therapy.

**Nickel in Urine**

The mean concentration of nickel in the urine of 107 normal subjects measured in our laboratory was found to be 2.0 µg per 100 ml with a standard deviation of ±1.1 over an eight-hour working period (table I). Statistical analysis of the data has led to the conclusion that only one specimen in 50 selected from a normal population will be found to exceed a value of 5.3 µg per 100 ml of urine. This value was therefore selected as the upper limit of normal. In 10 years, 18,815 routine analyses were undertaken on urine specimens collected over eight-hour periods. All of these specimens had a nickel concentration below six µg per 100 ml of urine. From a practical standpoint, measurements of nickel concentration in urine have proved to be more satisfactory than estimations of total nickel excretion because of the difficulty of obtaining from industrial workers reliable estimations of the volume of urine excreted within stipulated periods of time. Furthermore, the time-saving factor has proved important in critical cases.

When we first undertook to treat patients exposed to nickel carbonyl, the only available chelating drugs were BAL (dimercaprol), d-penicillamine, and calcium disodium ethylenediaminetetraacetic acid (EDTA). Our studies on experimental animals showed that administration of d-penicillin had doubtful antidotal effectiveness and produced severe toxic side reactions; EDTA provided no antidotal effects, and BAL was only partially effective. With BAL, the
In the early 1950s, attention was attracted to a number of metabolic studies on dithiocarbamates that were appearing in the literature at that time. These studies were of especial interest since sodium diethyldithiocarbamate (Dithiocarb) is the chemical used as the nickel-binding reagent in a routine method for measuring nickel in urine. The metal-binding property of the dialkyldithiocarbamates was first reported in Delepine in 1908. It was not, however, until 25 years later that this property found application in analytical chemistry and led to the development of a method for the measurement of trace amounts of nickel. The structures of sodium diethyldithiocarbamate and its nickel chelate were studied by Vaciago and Fasana and are portrayed in figure 2. The nickel in the

<table>
<thead>
<tr>
<th>Normal population (pg/100 ml)</th>
<th>Mean concentration</th>
<th>One analysis in 50 (calculated)</th>
<th>18,815 Routine analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 ± 1.1</td>
<td>&gt; 5.3</td>
<td>&lt; 6.0</td>
<td></td>
</tr>
</tbody>
</table>
complex is described as being a squarecplanar (dsp$^3$) hybrid.

Domar and associates$^4$ found that Dithiocarb was involved in the metabolism of disulfiram (Antabuse). After the administration of Antabuse to man and experimental animals, Dithiocarb was found to be present in blood, tissues, urine, bile, and feces. The metabolic pathway of Antabuse, and presumably Dithiocarb, is shown in figure 3. A portion undergoes oxidation to form free and ethereal sulfates as well as metal complexes.

The chemical and biologic properties of sodium diethyldithiocarbamate (Dithiocarb) are given in table II.$^{19}$ Recognition of the nickel binding and biologic properties of the dithiocarbamates as well as their low toxicity prompted the initiation of studies to determine their possible chemotherapeutic properties as an antidote to acute nickel carbonyl poisoning.

The therapeutic effectiveness of 13 alkyl dithiocarbamates was studied in experimental animals receiving lethal inhalations of nickel carbonyl.$^{23}$ Of the various derivatives tested, sodium diethyldithiocarbamate proved to be the least toxic and one of the most effective. The LD$_{50}$ value for the sodium salt administered to mice and rats was 1.5 g per kg of body weight.$^{23}$

![Figure 2. Chelation of nickel by Dithiocarb.](image)

![Figure 3. Metabolism of disulfiram and Dithiocarb.](image)
TABLE II
Properties of Sodium Diethyldithiocarbamate Trihydrate (Dithiocarb)

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecular weight</th>
<th>Appearance</th>
<th>Melting point</th>
<th>Solubility</th>
<th>Stability</th>
<th>LD₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>S¹I (C₂H₅)₂N-C-S Na • 3H₂O</td>
<td>225.3</td>
<td>White crystalline solid</td>
<td>90 to 92°C</td>
<td>Soluble in water, methanol, ethanol, and acetone</td>
<td>Insoluble in ether and benzene</td>
<td>Mice and rats (i.p. and oral) 1.5 g/kg body weight</td>
</tr>
</tbody>
</table>

A 10% aqueous solution of sodium diethyldithiocarbamate trihydrate yields a pH value of 11.6 at room temperature. This solution may be buffered with monosodium phosphate to 7.4. At pH concentrations lower than 7.4, the mixture becomes turbid and decomposes, developing an odor of H₂S.

Antidotal Activity of Dithiocarb in Mice and Rats

The antidotal activity of Dithiocarb in mice and rats exposed to nickel carbonyl are given in table III. Of 30 mice exposed to nickel carbonyl vapors in a concentration of six ppm for 30 minutes, only six survived a period of five days following exposure. In concentrations of eight ppm and above, practically all of the exposed mice died. It will be seen in the table that of 30 mice exposed to nickel carbonyl in a concentration amounting to several times the LD₁₀₀ dose and receiving Dithiocarb parenterally in dosages of 50 and 100 mg per kg of body weight immediately after exposure, all of the animals survived. It will also be seen that of 390 mice exposed to nickel carbonyl at 10 ppm, all but two died within five days. On the other hand, of mice exposed to this same concentration of nickel carbonyl and given Dithiocarb parenterally, all survived for five days and were in good health.

It will also be seen in table III that of 30 rats exposed to nickel carbonyl in a concentration of 67 ppm for 30 minutes, only 11 survived for five days. In concentrations of 168 ppm and above, none survived. However, rats exposed to lethal concentrations of nickel carbonyl and given Dithiocarb parenterally in doses of 50 and 100 mg per kg of body weight, all survived.

The dramatic effectiveness of Dithiocarb in counteracting the lethal effects of nickel carbonyl in experimental animals led us to employ this chemical in humans who were accidentally exposed to nickel carbonyl.

In 1957, our first patient, who was severely exposed to nickel carbonyl, was treated with Dithiocarb. After I served as the first control subject by taking a test dose of Dithiocarb without ill effects, Dithiocarb was administered to a workman who had been accidentally sprayed with nickel carbonyl. This man (Patient D) had to be resuscitated by oxygen inhalation. Patient D received one g of Dithiocarb twice daily for 10 days after exposure. He became asymptomatic after the second day of hospitalization and developed no delayed reactions. The nickel concentrations in Patient D’s urine during the 16 days after exposure are shown in figure 3. It will be noted that the initial concentration of nickel in the patient’s urine was 200 µg per dl. The highest concentration we have observed in an exposed person was 247 µg per 100 ml.

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Number Surviving 5 Days</th>
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<tbody>
<tr>
<td></td>
<td>MICE</td>
</tr>
<tr>
<td></td>
<td>Untreated</td>
</tr>
<tr>
<td>6</td>
<td>6/30</td>
</tr>
<tr>
<td>8</td>
<td>0/30</td>
</tr>
<tr>
<td>10</td>
<td>2/390</td>
</tr>
<tr>
<td>16</td>
<td>0/30</td>
</tr>
<tr>
<td>24</td>
<td>0/30</td>
</tr>
<tr>
<td>67</td>
<td>11/30</td>
</tr>
<tr>
<td>105</td>
<td>6/30</td>
</tr>
<tr>
<td>168</td>
<td>0/30</td>
</tr>
<tr>
<td>266</td>
<td>0/30</td>
</tr>
</tbody>
</table>

*Nickel carbonyl was administered by inhalation for 30 minutes.
On figure 3 are plotted the concentrations of nickel in urine from 13 patients with nickel carbonyl poisoning treated with Dithiocarb. The total amounts of Dithiocarb administered to each of these men ranged from 6 to 28 g during periods from two to 14 days. The administration of Dithiocarb was attended by nickeluresis. Dithiocarb therapy was maintained until the concentrations of nickel in the urine reached normal levels. No adverse effects have been observed from the administration of Dithiocarb to these subjects or to normal volunteers.\textsuperscript{12}

During the past 30 years, more than 375 persons exposed to the inhalation of nickel carbonyl vapor have been treated under our supervision with Dithiocarb. To our knowledge, no death from acute nickel carbonyl poisoning occurred in any person who received adequate Dithiocarb medication within four days after exposure. It should be noted that patients receiving Dithiocarb who ingest alcoholic beverages may experience
symptoms similar to those described for Antabuse.\textsuperscript{12}

Certain manufacturing plants using nickel carbonyl in their operations measure the concentration of nickel in urine of workmen at the end of each working period. In those instances in which increased concentrations of nickel above 10 $\mu$g per 100 ml of urine are reported, the workmen are given Dithiocarb as a preventive measure even though they may have developed no symptoms of exposure or may not have been aware that they had been exposed to nickel carbonyl. Such preventive measures have proved to be exceptionally effective in reducing the hazards of exposure.

**Guide to Treatment of Acute Nickel Carbonyl Poisoning**

The following procedure has been found to be effective for subjects known or suspected of having been exposed acutely to hazardous concentrations of nickel carbonyl.\textsuperscript{13,15} If there is any doubt regarding the extent or severity of exposure of a worker to nickel carbonyl, an initial course of one g of Dithiocarb is given in divided doses. (Formerly two grams were given.) When given in one dose, nausea occasionally develops. This may be lessened by administering the Dithiocarb in divided doses as follows: 0.2 g of Dithiocarb with water every two minutes for five doses along with 0.2 g of sodium bicarbonate. If the symptoms of nickel carbonyl poisoning are minimal, decision regarding further therapy may be deferred until the results of the urine analysis for nickel are obtained.

If the initial eight-hour specimen of urine has a nickel concentration of less than 10 $\mu$g per 100 ml, the exposure may be classified as mild. In such cases, it is probable that delayed symptoms will either not develop or will be minimal. Most patients in this group are able to continue work, although a few may complain of fatigue and require rest. If severe delayed symptoms develop unexpectedly, such patients are hospitalized and given Dithiocarb in a dosage schedule outlined for the moderately severe group.

If the concentration of nickel in the first eight-hour collection of urine is above 10 $\mu$g but less than 50 $\mu$g per 100 ml, the exposure may be classified as moderately severe. Since delayed symptoms may develop in these patients, they should remain under careful observation for at least a week. Dithiocarb should be administered orally to these patients so that the total daily dosage on the first day of exposure amounts to between 15 and 20 mg per pound of body weight (35 to 45 mg per kg). For a man weighing 160 pounds (72.7 kg), the daily dosage is, therefore, between 2.5 and 3.3 g. The suggested dosage schedule is:

- 1.0 gram (five 0.2 g capsules) — 0 hour
- 0.8 gram (four 0.2 g capsules) — 4 hours
- 0.6 gram (three 0.2 g capsules) — 8 hours
- 0.4 gram (two 0.2 g capsules) — 16 hours

On subsequent days, Dithiocarb therapy should be continued in a dosage of 0.4 g every eight hours until the patients are free of symptoms and the concentration of nickel in urine has decreased to the normal range.

If the concentration of nickel in the first eight-hour collection of urine is above 50 $\mu$g per 100 ml, the exposure may be classified as severe. These patients are apt to be seriously ill and require hospitalization. Most of these patients can be maintained with oral Dithiocarb therapy as outlined for the moderately severe group. However, if the patient’s condition is critical, it is
suggested that Dithiocarb be administered parenterally* in an initial dosage of 12.5 mg per pound of body weight. Additional doses should be given in accordance with the clinical evaluation.

**COMMENTS ON DELAYED SYMPTOMS**

Initial symptoms including frontal headache, nausea, cough, dyspnoea, constriction in chest, etc., frequently pass off rapidly after the patients have received Dithiocarb. In some cases, the patients remain symptom-free for a period of a few hours to a week or more. During this quiescent period, it is essential that the subjects be observed carefully for the appearance of delayed reactions. In cases of severe exposure, the initial symptoms may merge gradually into the more severe delayed type. The delayed symptoms include a return of dyspnoea, cough, and sense of constriction over the sternum and epigastrium, as well as nausea, vomiting, cyanosis, sleeplessness, and delirium. Seriously ill patients usually have little or no fever. Oral temperatures rarely exceed 101°F (38.3°C). Fatalities usually occur between the 4th and 11th day after exposure.

**EFFECTS OF PROTRACTERED ADMINISTRATION OF DITHIOCARB**

Studies were undertaken to evaluate the toxicity and metabolic effects that may result from the daily administration of Dithiocarb to albino rats and beagle dogs in dosages of 30, 100, and 300 mg per kg of body weight for a period of 90 days. Throughout this period of observation, the animals receiving Dithiocarb were comparable in appearance, behavior, and appetite to the control group. No significant difference in the mean body weights of the test group were observed during the course of this study.

**ANTITUMORIGENIC EFFECTIVENESS OF DITHIOCARB**

Studies were undertaken to ascertain the possible antitumorigenic effectiveness of sodium diethyldithiocarbamate (Dithiocarb) on the development of tumors in rats following the muscular implantations of nickel subsulfide (Ni₃S₂). These tumors have histologic characteristics which suggest origin from striated muscle and have been classified as rhabdomyosarcoma. Most of the tumors metastasize.

In two separate studies over a period of two years, a total of 100 four-month old Fischer rats received muscular implantations of Ni₃S₂. Of this total, 50 rats (25 males and 25 females) were treated with Dithiocarb for a period of four to six weeks. Seventy-eight percent of the untreated rats developed sarcomas as compared to 32 percent of the treated rats (table IV).

Analyses of the data revealed a striking difference in the sex responsiveness to Dithiocarb. Of the 25 female rats with Ni₃S₂ implantations and treated with Dithiocarb, only 12 percent developed sarcomas as compared to 78 percent of the untreated rats.
sarcomas; of the male rats similarly treated, 52 percent developed sarcomas. The difference in sex response is statistically significant (p = 0.005).

The mechanism by which Dithiocarb causes an increased inhibition of tumorigenic activity in female rats as compared to males is speculative.

It is recognized that patients with implanted prostheses may on occasion develop malignant tumors. It seems probable that their development is related to the presence of nickel. It is suggested that in such circumstances, chelation therapy with Dithiocarb should be considered.

Summary

A brief review and summary has been presented of our studies which led to the therapeutic use of sodium diethyldithiocarbamate (Dithiocarb) in the treatment of nickel carbonyl poisoning.

References


19. Sunderman, F. W. and Sunderman, F. W., Jr.: Nickel poisoning. VIII. Dithiocarb: A new therapeuti...


