Efficacy of Sodium Diethyldithiocarbamate (Dithiocarb) in Acute Nickel Carbonyl Poisoning*

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ABSTRACT

A brief historical resume is presented on the use of dithiocarbamates for the treatment of persons exposed to nickel carbonyl. The specificity of the treatment is demonstrated in an industrial accident in which four men were simultaneously exposed to nickel carbonyl vapors. Three of the men received dithiocarb within 24 hours after exposure and the fourth was hospitalized by his family physician and treated for bronchopneumonia with antibiotics and without benefit of dithiocarb. The three workmen who received dithiocarb became symptomless and returned to work within 72 hours after exposure. The fourth man who had not received dithiocarb died within five days after exposure.

Introduction

Although poisoning from the inhalation of nickel carbonyl was recognized as early as 1903, nevertheless, the hazards from occupational exposure have been emphasized for only the past three or four decades. It may also be noted that specific therapy for acute nickel carbonyl poisoning has been available on a limited basis for only two decades. In the United States, the specific antidote, dithiocarb, is still categorized as an investigational drug.

This presentation is primarily concerned with acute nickel carbonyl poisoning and specifically with the development of sodium diethyldithiocarbamate (dithiocarb) as an antidote. For purposes of historical perspective, reference will be made to some of our early work on prevention, diagnosis and treatment of acute nickel carbonyl poisoning since the development in our laboratory of dithiocarb as a chemotherapeutic agent was, in large measure, dependent upon these early studies.

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, acute and chronic* studies were initiated at that time (and have been continued to the present) (1) to provide safeguards for the prevention of accidental exposure, (2) to develop...
methods for the early detection of poisoning in persons who might have been unknowingly exposed and (3) to establish therapeutic measures for the treatment of those exposed.

**Prevention**

The early efforts for prevention of accidental exposure to nickel carbonyl entailed not only careful engineering and architectural design of working areas to ensure adequate ventilation and to guard against spillage and leakage, but also the development of a monitoring system to make certain that the concentrations of nickel carbonyl in the working environment did not exceed the maximal allowable limits for safety.

Obviously, the simplest method of determining the presence of a noxious substance in air is its detection by odor. However, nickel carbonyl, even in highly hazardous concentrations, has only a mild, non-penetrating odor, often described as "sooty" or "musty." Thus, its presence is likely to be unnoticed by those unfamiliar with it. For example, in an accident that occurred in an oil refinery 25 years ago in which more than 100 persons were exposed to nickel carbonyl, there was no suspicion of exposure until the workmen started to become 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 we called "the snifter," had a sensitivity of less than 1 ppm and was reasonably precise. The system was later modified and adapted for the continuous, automatic monitoring of working areas. Eventually, the procedure was replaced by conductimetric 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 materials, easy to manipulate and adaptable for routine purposes. To meet these criteria, the colorimetric method of Alexander, Godar and Linde was modified by Kincaid, Stanley, Beckworth and Sunderman and became well adapted for the routine analysis of nickel in urine.

In our early studies of nickel metabolism in dogs, it had been found that under normal conditions, approximately 90 percent of ingested nickel was excreted in the feces and only 10 percent in the urine (figure 1). However, when balance studies were made on dogs exposed to nickel carbonyl, it was found that during the first three days after exposure more than twice as much nickel was excreted in the urine as in the feces. This observation that there was a sharp increase in the nickel excretion in urine immediately after exposure to nickel carbonyl proved to be of major practical value and led to the development of procedures for detecting exposure in workers to minimal amounts of nickel carbonyl in concentrations which were too low to produce acute symptoms. Simple measurements of the nickel concentration in 100 ml of urine proved to be more satisfactory than the more laborious procedure of determining the total amount of nickel excreted in 24
hours. Moreover, the time-saving factor proved to be important in critical cases.* In several industrial plants, procedures were set up by which workmen in nickel carbonyl areas would leave a specimen of urine for nickel analysis at the close of each working day. If the concentration of nickel exceeded set limits, the workman would be placed under observation and given medication if needed. Owing to cost factors, plant managers were at first reluctant to provide a urine testing service for employees in the nickel carbonyl areas; however, in the words of one manager, “Experience over the years has shown that this service has paid off handsomely in safeguarding the health of our employees.”

Treatment

When we first undertook to treat patients exposed to nickel carbonyl, the only available chelating drugs were BAL (dimercaprol), d-penicillamine and EDTA (calcium disodium ethylenediaminetetraacetic acid). Our studies on experimental animals showed that (1) administration of d-penicillamine had doubtful antidotal effectiveness and produced severe toxic side reactions; (2) EDTA provided no antidotal effects; and (3) BAL was only partially effective. With BAL, the LD\textsubscript{50} value in rats exposed to nickel carbonyl is increased by a factor of approximately two.

In an accident in 1954 in which 36 persons were exposed to nickel carbonyl, received BAL. Two of the 36 persons died and one of those who died had received BAL. In the opinion of the attending physicians, the administration of BAL was beneficial in 31 of the patients receiving BAL and may have been life-saving in several.

In the early 1950’s, our attention was attracted to the metabolic studies on dithiocarbamates that were appearing in the literature at that time. These studies were of especial interest to us since sodium diethylidithiocarbamate is the chemical used as the nickel-binding reagent in our routine method for measuring nickel in urine. In 1949, Domar and coworkers reported diethylidithiocarbamate to be a metabolic reduction product of Antabuse (disulfiram). After the administration of Antabuse to man and experimental animals, these investigators demonstrated that dithiocarb was present in the blood, tissues, urine, bile and feces. The metabolic pathway of Antabuse, and presumably dithiocarb, is shown in figure 2. Dithiocarb is partially excreted unchanged in urine and bile. A portion undergoes oxidation to form free and ethereal sulfates as well as metal complexes. The structure of the nickel chelate

* The concentration of nickel in urine samples obtained from 69 normal persons was 1.1 µg per dl (S.D. ± 0.9). A statistical analysis of these data led to the conclusion that only one specimen in 50 selected from a normal population will be found to exceed a value of 5 µg per dl. The value was therefore selected as the upper limit of normal.
of diethyldithiocarbamate is depicted in figure 3.14 Excepting for the methyl groups, the nickel in the complex is a square coplanar hybrid.

Hald, Jacobsen and Larsen in 1948 and 19526,7 showed that the diethyldithiocarbamates were relatively non-toxic for mice and rats,—the LD50 value for the sodium salt being approximately 1.5 g per kg of body weight. Goth and Robinson5 noted that the dithiocarbamates displayed antidotal activity by showing that the bismuth salt protected mice against Type I pneumococcal infections. In addition, Garattini and Leonard4 found dithiocarb to be an effective in vitro inhibitor for the growth of Mycobacterium tuberculosis.

Recognition of the nickel binding and biologic properties of the dithiocarbamates as well as their low toxicity prompted us to initiate 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.16 Of the various derivatives tested, sodium diethyldithiocarbamate proved to be the least toxic and one of the most effective.

Antidotal Activity of Dithiocarb in Mice and Rats

The antidotal activity of dithiocarb in mice exposed to nickel carbonyl is given in table I. Of 30 mice exposed to nickel carbonyl vapors in a concentration of 6 ppm for 30 minutes, only six survived a
period of five days following exposure. In concentrations of 8 ppm and above, practically all of the exposed mice failed to survive. 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.

The antidotal activity of dithiocarb in rats exposed to nickel carbonyl is shown in table II. It will be seen 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. When administered orally by stomach tube in dosages of 10 and 100 mg per kg of body weight immediately after nickel carbonyl exposure, dithiocarb provided moderate protection. It would seem reasonable that even better protection might have been afforded if sodium bicarbonate had been administered with the dithiocarb. Similar studies, not tabulated here, on rabbits and dogs exposed to nickel carbonyl and given dithiocarb intravenously resulted in complete recovery from nickel carbonyl poisoning.

**Nickel Balance Studies in Rats**

The results of the nickel balance studies in 12 normal rats and in 24 rats exposed to nickel carbonyl at a concentration of 33 ppm for 30 minutes are shown in figure 4. At this concentration, all rats survived for at least three days. Twelve of the exposed rats were left untreated; the remaining 12 received dithiocarb in a dosage of 30 mg per kg of body weight intraperitoneally immediately after exposure. In figure 4 are portrayed the average amounts of nickel ingested in the food and excreted in the stool and urine in each of the three groups during the three-day metabolic period. In the control rats, approximately 80 percent of the ingested nickel was excreted in the stool and 20 percent in the urine. The rats exposed to nickel carbonyl

### TABLE I

**Antidotal Activity of Dithiocarb in Mice**

<table>
<thead>
<tr>
<th>Ni(CO)₄ concentration (p.p.m.)</th>
<th>No. of mice surviving 5 days</th>
<th>Treated with dithiocarb i.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Un-treated</td>
<td>50 mg./kg.</td>
</tr>
<tr>
<td>6</td>
<td>6/30</td>
<td>30/30</td>
</tr>
<tr>
<td>8</td>
<td>0/30</td>
<td>30/30</td>
</tr>
<tr>
<td>10</td>
<td>2/390</td>
<td>390/390</td>
</tr>
<tr>
<td>16</td>
<td>0/30</td>
<td>30/30</td>
</tr>
<tr>
<td>24</td>
<td>0/30</td>
<td>30/30</td>
</tr>
</tbody>
</table>

*Nickel carbonyl was administered by inhalation for 30 minutes.*

### TABLE II

**Antidotal Activity of Dithiocarb in Rats**

<table>
<thead>
<tr>
<th>Ni(CO)₄ concentration (p.p.m.)</th>
<th>No. of rats surviving 5 days</th>
<th>Treated with dithiocarb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Un-treated</td>
<td>50 mg./kg.</td>
</tr>
<tr>
<td>67</td>
<td>11/30</td>
<td>30/30</td>
</tr>
<tr>
<td>105</td>
<td>6/30</td>
<td>30/30</td>
</tr>
<tr>
<td>168</td>
<td>0/30</td>
<td>30/30</td>
</tr>
<tr>
<td>266</td>
<td>0/30</td>
<td>30/30</td>
</tr>
</tbody>
</table>

*Nickel carbonyl was administered by inhalation for 30 minutes.*

I.p.

<table>
<thead>
<tr>
<th></th>
<th>oral</th>
<th>50 mg./kg.</th>
<th>100 mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>1/10</td>
<td>7/10</td>
<td>9/10</td>
</tr>
<tr>
<td>266</td>
<td>0/10</td>
<td>1/10</td>
<td>4/10</td>
</tr>
</tbody>
</table>
Figure 4. Nickel balance studies in rats. Each group consisted of 12 rats. Nickel carbonyl inhalation was administered at a concentration of 33 ppm for 30 minutes after which 12 rats were given 30 mg per kg dithiocarb intraperitoneally.

and left untreated developed a positive nickel balance averaging 45 μg per rat during the metabolic period. It may be noted that the food consumption was exceedingly low in these rats since most of them were too sick to eat. On the other hand, in the rats exposed to nickel carbonyl and treated with dithiocarb, the food consumption was essentially normal.

The urinary excretion of nickel in the treated rats was more than twice that of the control rats and approximately twice that of the untreated exposed rats. Likewise, there was a marked increase in the fecal excretion of nickel in the treated rats. It will be observed that dithiocarb increased the excretion of nickel to the extent that a normal nickel balance was achieved.

In 1957 our first patient, who was severely exposed to nickel carbonyl, was treated with dithiocarb. After I had 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 5. It will be noted that the initial
concentration of nickel in the patient's urine was 200 µg per dl. This is the highest concentration we have ever observed in any exposed person.

During the past score of years, more than 350 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 two to three days after exposure. It is also noteworthy that the administration of dithiocarb is not attended by the protracted undesirable side effects that are observed with chelating drugs such as BAL and d-penicillamine. However, patients receiving dithiocarb who ingest alcoholic beverages may experience symptoms similar to those described for Antabuse.

Efficacy of Dithiocarb

The efficacy of dithiocarb as a specific antidote for acute nickel carbonyl poisoning is demonstrated by the outcome of an accident that occurred in a chemical plant in which nickel carbonyl was used as a catalyst in the manufacture of acrylic plastics. Four workmen unbolted a flange on one of the scrubbers used in the manufacturing process in order to make necessary repairs. Although the four workers were aware of the hazards of exposure to nickel carbonyl, nevertheless, since the scrubber was not in operation, it did not occur to them that they might still become exposed to the vapors that were trapped within the scrubber. A "sooty" odor was noted by the men on removal of the flange; however, this was interpreted by them to be due to the penetrating oil used in loosening the bolts.

The workmen completed their assigned duties and returned to their respective homes where all of them soon developed severe respiratory symptoms. When the four men failed to report for work the next afternoon and reported sick with respiratory symptoms, an alert safety director surmised that perhaps they had been exposed to nickel carbonyl. Stat urinalyses for nickel were made on specimens from all of the men and revealed concentrations of nickel in the range of 50 µg per dl (45 to 58). From these analyses, it was inferred that all of the men suffered from acute nickel carbonyl poisoning and were subjected to approximately the same severe degree of exposure. The safety director requested all of the men to go immediately to the industrial dispensary for examination and to receive dithiocarb medication. Three of the men went and were immediately administered dithiocarb. These three men became symptomless and returned to work within 48 hours after having received the medication. In the meantime, the fourth workman consulted his family physician who gave him an injection of penicillin and had him admitted to the community hospital.

Case Report

The patient, W. P., 47 years of age, was admitted to his community hospital with cough, nausea, vomiting and weakness. Soon after exposure he developed cough, hot and cold sweats, chills, fever, vertigo and chest pains. His past medical history included treatment for prostatitis and for symptoms suggestive of peptic ulcer three years previously and for influenza one year previous to the present administration. The examining physician noted that the patient was well nourished, weighing 210 pounds; his blood pressure was 150/84 mm of mercury; pulse rate on admission was 88 and respiration 22 per minute; his temperature was 100.1°F. The chest examination revealed bronchial breathing and the chest x-ray revealed diffuse densities throughout both lung fields which were interpreted as bronchopneumonia and pulmonary edema. An electrocardiogram was reported to be within normal limits excepting for a tachycardia of 104 beats per minute. The hemoglobin concentration was 15.9 g per dl; hematocrit 40 percent; leucocytes, 12,400 per cmm.

The patient was treated with antibiotics and tranquillizers. The attending physicians were reluctant to administer dithiocarb since this was an investigative drug with which they had had no experience. On the fourth day after exposure when the patient was
moribund, it appears that a minimal amount of dithiocarb was offered to the patient but that he was unable to swallow the capsules. No dithiocarb was administered intravenously. The patient died on the fifth day after exposure. Prior to death, a tracheostomy was performed.

Pathologic Findings

At autopsy, the external examination revealed a tracheostomy opening from which fluid and blood escaped on pressure. The lungs had a combined weight of 2,430 g. The trachea and bronchi contained a generous amount of sanguineous mucoid material. The lungs were firm on palpation and sectioning revealed marked congestion. The heart was enlarged, weighing 540 g. The myocardium appeared normal. A small amount of coffee-brown liquid material was found in the stomach. The liver, spleen, adrenals and pancreas showed no significant abnormalities.

The most significant microscopic changes were observed in the lungs. Most prominent among these were hyaline membrane formation, damage to alveolar lining cells and dilatation of alveolar capillaries secondary to congestion (figure 6). The alveoli contained granular, pink edema fluid, occasional acute inflammatory cells and a moderate number of desquamated pneumocytes. Attached to the alveolar septae in numerous areas were hyaline membranes composed of eosinophilic homogeneous material (figure 7). The alveolar lining cells in most areas displayed either degenerative changes or were totally absent leaving denuded and dilated capillaries and interstitial cells as alveolar landmarks. Occasional pneumocytes were hypertrophied or had prominent nuclei and nucleoli. Mitoses and giant cells were seen only rarely. The alveolar septae were widened owing mainly to the capillary dilatation and interstitial edema. Inflammatory cells and fibroblasts were present within the septas, but this feature was not prominent.

The histologic features appeared to be those of an acute interstitial pneumonitis displaying mainly degenerative rather than reactive or regenerative changes.

The histologic findings in the liver consisted of congestion of central and portal vein branches with slight central hepatodegeneration. An inflammatory cell reaction was not conspicuous. Sections of brain and kidneys revealed only congestive changes.

Measurements of nickel in the lung and liver tissues obtained at autopsy were 11 and 6 times greater than the average concentrations of lung and liver tissues obtained at autopsy from persons who had died suddenly from causes not related to nickel exposure (table III).

The history, physical examination and laboratory findings in the deceased workman who had not received dithiocarb left no doubt that this workman died of acute nickel carbonyl poisoning.

Summary

In summary, reference has been made to some of the early studies which led to the development of dithiocarb as a specific antidote for acute nickel carbonyl poisoning. A case report was presented to illustrate not only the therapeutic effectiveness of dithiocarb in treating nickel carbonyl poisoning but also to emphasize the fact that the diagnosis of acute nickel carbonyl poisoning may be readily overlooked in hospital practice. In any patient suffering from an undiagnosed fulminating

| TABLE III |
| Nickel in Tissues |
| Wet Weight (mg/100 g) | Dry Weight (mg/100 g) |
| Lung | Liver | Lung | Liver |
| W.P. Ni(CO)\(_4\) poisoning | 17.3 | 5.3 | 115.0 | 20.7 |
| Mean of 4 control subjects | 1.59 | 0.87 | 8.6 | 2.9 |
FIGURE 6. Section shows marked congestion of alveolar capillaries and venules. Alveolar spaces contain granular proteinaceous material (× 280).

FIGURE 7. Section shows intra-alveolar edema with hyaline membrane lining the alveolar wall (× 380).
ing pneumonitis, consideration should be given to the possibility that the patient might have been exposed unknowingly to nickel carbonyl.

Acknowledgment

Thanks are extended to Dr. Geoffrey Kent and Dr. Roy Smith for their comments on the histopathology and to Dr. F. William Sunderman, Jr. for nickel analyses of the tissues.

References

10. Personal communication.