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# Prophylactic Chelation Therapy: A Review of the Literature

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## Introduction

The present paper reviews the available medical and scientific evidence concerning prophylactic chelation therapy as one of the means to control occupational lead intoxication. Prophylactic chelation is herein defined both as the routine use of chelating or similarly acting drugs to prevent elevated blood lead levels in workers who are occupationally exposed to lead or as the use of these drugs to routinely lower blood lead levels to predesignated concentrations believed to be "safe." A number of studies have been published on the use of $CaNa_2$ EDTA, a chelating agent and penicillamine in the therapy of lead intoxication. Most authorities agree that chelating or similarly acting agents have a proper place in the therapy of the acute symptomatology of severe lead intoxication, a condition accompanied by pronounced gastroenteric, neurologic and other symptoms. The primary focus of this review deals with questions of the health risk involved in chelation therapy and particularly with whether there are adequate assurances of safety to condone prophylactic chelation therapy, particularly under conditions of continued exposure to lead.

Review and Discussion of the Literature

Sidbury, Bynum and Fetz[1] studied the effects of oral and intravenous $CaNa_2$ EDTA upon urinary lead excretion. Study subjects were 5 adults and 2 children who either had symptoms of lead poisoning or excessive amounts of lead in the blood or urine. Intravenous and oral doses were administered for periods of 5 days; both routes of administration were accompanied by increased urinary lead excretion compared to pre-treatment values. Urinary lead excretion following intravenous $CaNa_2$ EDTA was greater than following oral administration. Gastrointestinal absorption of the drug was suggested by increased urinary lead excretion following oral administration; however, formation of a lead EDTA complex in the gut with subsequent absorption could not be ruled out. One patient exhibited side reactions, abdominal pain and loose stools, following oral medication. No long term followup of study subjects was conducted.

Cotter[2] examined the treatment of lead poisoning with oral $CaNa_2$ EDTA. The effect of one week's therapy upon blood lead, urine lead and serum electrolytes in 4 men employed in the painting trades was presented. Symptoms of lead intoxication generally decreased following therapy, as did blood lead. Although serum electrolytes remained within normal limits following therapy, there was a tendency for magnesium and copper to decrease after medication suggesting that long term chelation therapy may affect metabolism of these metals. Long term followup evaluations

were not made and judging from the results of the followup blood lead analyses in some subjects, which are reported as zero, there is some doubt as to the adequacy of the analytic procedures employed in this study.

Bradley and Powell[3] described the use of oral $CaNa_2$ EDTA in the therapy of childhood lead intoxication. Study subjects had a documented history of lead intoxication and all 5 children evaluated were hospitalized during this investigation. Patients were given oral $CaNa_2$ EDTA at 75 mg/kg/day for a period of 9 days. The medication produced significant increases in urinary lead excretion in all patients compared to pretreatment levels with maximum urinary excretion occurring between the second and fourth day of therapy. Blood lead levels in all children decreased following treatment. T wave changes in the electrocardiograms of 4 out of 5 patients were observed which were believed to be related to the therapy. In 3 patients an improvement in appetite and a decrease in irritability was observed following treatment. Bradley and Powell concluded that oral $CaNa_2$ EDTA may have some value in the treatment of chronic lead poisoning in children but no data are presented to assure the safety of long term drug administration.

Kehoe[4] warned against the misuse of $CaNa_2$ EDTA for the prophylaxis of lead poisoning in 1955. He noted that prophylactic remedies before EDTA became available had been tried without success and

that these actions were often used in place of adequate environmental controls to reduce lead exposure in the workplace. Kehoe indicated that simple and relatively inexpensive medical prophylactic procedures would be favored by management rather than expending the necessary funds to install safe process design and engineering controls. Kehoe raised questions as to whether the apparent short term benefits of chelation therapy outweighed the long term almost certain hazards of its use. In particular, concern was expressed that prolonged administration of chelating agents had the potential to disturb metabolism of minerals in the body. Kehoe considered that subjecting workers occupationally exposed to lead to prophylactic chelation was "rash and irresponsible."

Sidbury[5] reported on the treatment of lead poisoning with $CaNa_2$ EDTA. Cases of men occupationally exposed to lead who were given oral $CaNa_2$ EDTA were included in this study. One man was treated in the plant dispensary but was not removed from exposure. Although symptoms were relieved as a result of therapy, symptoms of lead poisoning recurred in about 3 months after treatment. Sidbury did not consider it possible to differentiate between the portion of lead in the urine which had been chelated in and absorbed from the gastrointestinal tract from that portion which had been chelated in the blood or tissues. Sidbury also warned against giving oral chelating agents under conditions of continued lead exposure or in instances of moderate

to severe lead poisoning. The effectiveness of EDTA therapy in instances of clinical lead poisoning was demonstrated. No significant adverse effects were reported in over 35 patients given oral or IV chelation therapy with EDTA. No followup studies were presented, however, to assure the safety of prophylactic chelation during continued lead exposure.

Manville and Moser[6] examined the effect of oral $CaNa_2$ EDTA upon lead in the blood and urine of battery workers. Twelve men were given oral medication for 5 days a week for 2-3 weeks at a dosage of 60 mg/kg/day. Three of these study subjects had a history of acute lead poisoning. Symptoms of lead intoxication such as constipation, fatigue, poor appetite and difficulty sleeping were reduced as a result of the medication. After one week of treatment average blood lead levels dropped by 10 ug/100ml and by the end of the third week blood lead levels dropped by another 10 ug/100ml. However, 3 subjects showed an elevated blood lead level at the end of the experiment compared to the beginning. This may partially be explained by continued exposure to lead on the job during the study period. Even repeated courses of therapy were not considered sufficient to rid the body of lead stores which had been accumulated over many months or years. Excretion of lead in the urine was approximately doubled as a result of the medication. No long term followup of men given prolonged treatment with the drug is presented.

Bell et al[7] studied 24 hour fecal and urinary lead excretion rates in 3 men with occupational lead poisoning before, during and after treatment with $CaNa_2$ EDTA both orally and intravenously. Subjects were removed from exposure during the course of the study. Combined urine and fecal lead excretions in these men were increased by a factor of 2-3 while receiving therapy. Both urinary and fecal lead excretions were increased during oral treatment. However, during IV therapy urinary lead excretion was greatly increased - while fecal lead excretion was diminished. Combined fecal and oral lead excretion during oral therapy was about two thirds that compared to the same daily dose intravenously. No followup of men receiving long term chelation therapy is presented.

Shiels, Thomas and Kearley[8] evaluated the treatment of lead poisoning by oral $CaNa_2$ EDTA. Five adult subjects with industrial lead poisoning were studied. In adults dosages were given at 4 g/day for several days, followed by a rest period of 7 days and an additional course of therapy similar to the first. All but one of these individuals were hospitalized during the study. In addition, the effectiveness of oral therapy was also evaluated in 14 ambulatory subjects. The subjects were removed from hazardous exposure prior to treatment. Oral $CaNa_2$ EDTA was considered likely to increase the absorption of lead from the gastrointestinal tract in instances where exposure to lead continued to occur during therapy due to the probability of additional lead ingestion in such circumstances. Oral medication caused a 5 to 20-fold increase

in urinary lead excretion which greatly exceeded the quantity of lead in circulating blood prior to treatment, suggesting a mobilization of lead from the bone. Blood lead levels tended to fall immediately following treatment, but in some cases this was followed by a rise in blood lead concentrations. Oral medication generally reduced the frequency of lead symptoms such as fatigue, weakness and loss of appetite. In one case, however, headache developed during the first 2 days of therapy. One case of a death in a woman with lead poisoning given IV EDTA reported in the literature in which the treatment was believed to have accelerated the fatal outcome was discussed. Within the scope of the study, no serious untoward effects of oral EDTA were found. This investigation did not evaluate the long term effects of oral chelation under conditions of continued lead exposure.

Holt[9] reviewed the treatment of lead absorption in industry. The author recognized that at high dosages $CaNa_2$ EDTA can cause damage to the kidney. Case reports were presented of 101 individuals who received oral EDTA at 4 grams per day for 5 days, followed by a rest period of from 5 to 10 days after which a second course of therapy was given. When used in this manner the procedure appeared to be reasonably safe. In three workers, however, symptoms were reported during the course of treatment. The importance of careful monitoring for kidney function was also stressed. Each patient had a urinalysis before the course of treatment and on the third and

fifth days during each five day course of medication. Even at the dosage given, 9% showed albumin or red blood cells in the urine indicating that some damage to the kidneys, perhaps reversible, had occurred. When this occurred, the second course of medication was not initiated until the urine had returned to normal which it did in all instances. However, in three cases, urine pathology reappeared when the second course of therapy was begun and in these instances the dosage was reduced. Among the complaints and effects that were noted in workers taking and attributed to this medication were leg cramps, abdominal pain, diarrhea, vomiting, malaise, weakness, constipation, increased muscle cramps, arthritic pain and urinary pathology. All told, about 30% of the individuals taking the drug experienced some adverse symptoms. Holt expressed the opinion that with oral $CaNa_2$ EDTA treatment individuals could continue working in the lead industry without endangering their health. However, he also noted that in a few persons exposed to lead and given oral $CaNa_2$ EDTA, renal complications may occur. Further, no evidence is presented to assure that routine, prolonged administration of oral $CaNa_2$ EDTA was safe, particularly under conditions of continued lead exposure.

Miller[10] reviewed the use of EDTA therapy in persons with excessive lead absorption from industrial exposure. EDTA does not appear to enter cellular components in the blood and the concentration in the spinal fluid is below that found in the blood. Damage to the kidneys has been observed in men given the drug and in animals

when relatively large doses were given over prolonged periods of time. Blood lead levels may rise following intravenous administration of the drug but without apparent adverse effects. This is usually followed by a decrease in blood lead with excretion of the lead chelate complex but this may be followed by a rise in blood lead level as lead from the skeleton is mobilized into the soft tissues. This raises questions as to the potential toxic effects to critical organs due to this mobilization. Persons undergoing chelation therapy should be checked frequently for the possible occurrence of renal damage. Miller did not feel that prophylactic use of EDTA to prevent lead intoxication can be condoned because prophylaxis can only be achieved by controlling the source of exposure by proper industrial hygiene techniques. The effects caused by prolonged administration of even low doses of $CaNa_2$ EDTA were not well understood and its use in this manner could not be supported. Use of prophylactic chelation was also likely to result in a false sense of security with ensuing failure to institute proper engineering and work practice controls.

Byers[11] reviewed cases of childhood lead poisoning who had been treated with $CaNa_2$ EDTA. While $CaNa_2$ EDTA is poorly absorbed from the gastrointestinal tract, the lead chelate is rapidly absorbed suggesting that oral medication should not be given under conditions of continued lead exposure. EDTA is reported to have caused kidney damage in both experimental animals and

in man. The author reviewed childhood lead poisoning cases all of whom had been treated with IV or IM EDTA during the acute phase of poisoning. Oral $CaNa_2$ EDTA did not shorten the period of coproporphyrinuria following cessation of IV medication. Oral $CaNa_2$ EDTA was less efficient than IV or IM therapy in correcting abnormalities in porphyrin metabolism during acute lead intoxication. Oral $CaNa_2$ EDTA given when lead is present in the gastrointestinal tract is considered by Byers to be a dangerous drug due to the increased absorption of the lead chelate. A case is described of a child mistakenly given oral $CaNa_2$ EDTA when his gastrointestinal trait contained lead and who shortly thereafter became comatose with convulsions followed by permanent and severe neurologic damage.

Burnett[12] described the use of oral $CaNa_2$ EDTA in the prevention of occupational lead poisoning. The plant in which this program was initiated was a relatively small operation involved in reclaiming lead primarily from batteries. Cases of lead poisoning had been common among the 16 men employed at this plant prior to initiation of this program in 1958. Efforts were made to reduce worker exposure as part of this program. Oral $CaNa_2$ EDTA was given prophylactically 5 days per week for two weeks followed by a 2 week rest period at which time the above dosage scheme was repeated. Vitamin-mineral supplements were also given to the employees. The medication program was supervised by the plant foreman. During the more than one year

that this program was operational no cases of acute lead poisoning were reported and no symptoms attributable to lead accumulation in the body were reported. Case reports are presented of two workers with no history of lead poisoning who took this medication with no evidence of plumbism or toxicity for a one year period. No blood lead levels are presented and there is no evidence of systematic medical evaluation for neurologic or renal function. It is noteworthy that the hemoglobin level in one of these workers was 12.9 gms and in the other 13.9 gms both suggesting adverse effects of lead upon the blood forming elements. In a third instance a man with two prior episodes of lead poisoning before his entrance into this program was presented. The hemoglobin in this man was 11.4 gms; red blood cell count was 3,880,000 and minimal basophilic stippling was present. Burnett indicated that there was no sign of toxicity or symptoms in this man despite objective evidence of moderately severe affects of lead upon the hematopoietic system. Although Burnett concluded that $CaNa_2$ EDTA is a safe and effective drug in the prevention of clinical lead poisoning, the data do not demonstrate the effectiveness of chelation therapy to protect against adverse effects of lead in instances of continued exposure. Further, it would be difficult to disentangle the benefits of improved engineering and work practices with respect to the decrease in cases of acute lead poisoning at this plant compared to the benefits of the drug per se.

Skinner[13] reviewed current knowledge and opinion concerning the problem of occupational lead exposure including the use of chelating agents in the therapy of lead intoxication. $CaNa_2$ EDTA was considered particularly useful in the treatment of acute phases of lead intoxication. Skinner noted that the routine use of this drug as a prophylactic measure to prevent lead absorption could not be condoned and that prophylaxis could only be achieved safely through control of sources of exposure by accepted industrial hygiene techniques. Medical measures could not be recommended as a substitute for adequate engineering measures to control lead exposure.

Williams, Matthews and Judd[14] reported on the results of a study in which 8 men with excessive lead absorption were given oral $CaNa_2$ EDTA for periods of 7 days. Urinary lead excretions increased to a maximum of 5-11 fold above baseline levels. In 5 patients blood lead levels decreased, in one blood lead remained the same and in one patient blood lead increased following therapy. Most men treated reported feeling better after receiving the medication. Evidence is presented to suggest that recently ingested lead may not be chelated in the gut, absorbed and subsequently excreted in the urine. This was based on observations in 3 men given chelating agents on Saturday in whom maximum lead excretion occurred on Sunday with no significant increase in urinary lead excretion on Monday when they returned to work, still on medication. This observation would appear to be at variance with other data presented in this paper. In this regard, about 5% of oral EDTA is absorbed

from the gastrointestinal tract, Williams et al explicitly warn against the unknown hazards of prolonged chelation therapy and explicitly warn against prophylactic chelation used to mask defects in engineering controls and personal protective equipment.

Oser, Oser and Spencer[15] evaluated the safety of Ca EDTA for use as a food additive. This compound is commonly used in foods in the range of 75 to 275 ppm. In large enough dosages EDTA is capable of interfering with the metabolism of or reducing body stores of mineral acids. Rats were given EDTA at levels of 50, 125, and 250 mg per kg per day in the diet for a period of 2 years. No adverse effects were observed on growth, food efficiency, hematologic examinations, prothrombin time, blood sugar, NPN or serum calcium. Autopsy studies did not reveal any significant differences in major organs between exposed and control groups. Dogs fed EDTA at 50, 100 and 250 mg per kg per day similarly showed no adverse effects following a one year feeding of this material. While these data provide some assurances of safety for long term administration of Ca EDTA in the animals tested, the effects of this agent in man under conditions of continued occupational lead exposure were not examined.

Foreman[16] reviewed the toxic effects of EDTA. Available studies in experimental animals suggested a wide spread between recommended therapeutic doses in man as contrasted to lethal doses in experimental animals. Concern has been expressed as to the possible

effects of prolonged administration of EDTA upon trace metal depletion in the body. However, those toxic side effects which have shown up in man are not those that are readily explainable by trace metal depletion. The most frequent and important side effect associated with EDTA is renal damage. Vacuolization of renal tubular cells resembling those seen in sucrose nephrosis have been observed at autopsy in two patients given disodium EDTA in the treatment of hypercalcemia; both patients died in renal failure following a 4 day course of treatment with EDTA. A number of autopsy studies have also demonstrated acute tubular neurosis in patients given EDTA in the treatment of lead poisoning. Clinical signs of kidney damage associated with EDTA include hematuria, proteinuria, polyuria and elevated BUN levels. Subsequent to these clinical reports studies in rats confirmed that nephrosis could be produced by administration of the drug; these lesions appeared to be reversible upon cessation of the drug administration. In Foreman's opinion there is a need for caution in the use of this drug and that patients given this medication should be given continued medical evaluation including daily urinalyses, blood urea nitrogen and postprandial blood sugar determinations.

Selander, Cramer and Hallberg[17] reviewed the use of penicillamine in the treatment of lead poisoning. In their discussion the authors pointed to the inherent risk of intravenous $CaNa_2$ EDTA particularly

with respect for its potential to induce severe renal damage. Selander et al also question the utility of oral $CaNa_2$ in the treatment of lead intoxication due largely to the relatively poor absorbability of the drug in the gastrointestinal tract.

Doolan et al[18] examined the nephrotoxicity of $CaNa_2$ EDTA and $CaNa_2$ DTPA in the rat. These studies were prompted by clinical cases of renal damage following administration of chelating agents primarily $CaNa_2$ EDTA. Male and female rats were given $CaNa_2$ EDTA and $CaNa_2$ DTPA intraperitoneally each day for 10 consecutive days and the animals were sacrificed 24 hours after the last injection. Control groups given intraperitoneal physiologic saline were included in this study. A number of histologic changes were seen in the kidneys of the exposed animals which consisted of well demarcated vacuoles in the cytoplasm of the epithelium of the proximal tubule of the kidney in the mildest cases which progressed to extrusion of cell contents and displacement of cell nuclei in the severest cases. Vacuolization was not accompanied by increases in serum creatinine or urea nitrogen. Administration of chelating agents to lead poisoned rats, however, did not appear to increase the damage to the kidneys that had been caused by the lead. Doolan et al, however, still considered it prudent to follow renal function closely in patients receiving chelating agents. In this regard, George[19] reported a case of lead poisoning in which renal damage was associated with intravenous administration of $CaNa_2$ EDTA.

Chisolm[20] reviewed the treatment of heavy metal poisoning including the use of chelating agents. In his opinion oral administration of $CaNa_2$ EDTA was not warranted in the treatment of heavy metal poisonings. The principal adverse side effect of $CaNa_2$ EDTA therapy is damage to the kidneys, particularly massive tubular neurosis. Abnormalities in cardiac conduction have also been observed during administration of this drug. Long term oral administration of $CaNa_2$ EDTA has been associated with a number of poorly defined untoward reactions including rashes and fever. Chisolm observed that monitoring of kidney function before and during administration of the drug is necessary. Among the side effects associated with penicillamine are nephrotic syndrome, leukopenia, neutropenia, coagulation deficits, erythematous rashes, altered collagen metabolism and fever. Children with chronic renal insufficiency should not be given penicillamine. Use of insufficient dosages of chelating agents compared to body loading with lead may actually increase the toxic effects of lead upon the body.

Goyer and Wilson[21] and Cramer et al[22] examined the effects of lead including $CaNa_2$ EDTA upon the kidneys. Lead poisoned rats were given intraperitoneal injections of $CaNa_2$ EDTA. Urinary excretion of lead and kidney lead content were significantly decreased 24 hours after a single injection of EDTA. At the same time, inclusion bodies (lead-protein complexes) in renal cell nuclei were found in various

stages of dissolution and migration out of the nucleus. Cytoplasmic vacuoles were observed which contained material that resembled portions of intact nuclear inclusions. Rats given 3 daily injections of EDTA did not have inclusion bodies in their kidney nuclei 24 hours after the last injection. These data indicate that nuclear inclusion bodies formed in the kidneys during lead poisoning are removed from renal cell nuclei by EDTA. Inclusion bodies are not observed in renal biopsies of men occupationally exposed to lead who have been repeatedly treated with chelating agents. Excretion of lead through the kidneys appears to be less in older men compared to younger men who have nuclear inclusion bodies in their renal tubule lining cells. These data suggest that chelation therapy reduces the ability of the kidneys to protect themselves against the toxic effects of lead by virtue of the effect of chelating agents upon lead induced inclusion bodies. This conclusion is further supported by observations by Chisolm[23] that renal tubular dysfunction may follow EDTA administration in lead poisoned children.

Lilis and Fischbein[24] reviewed the subject of chelation therapy among lead exposed workers. They concluded that chelation therapy was useful for the treatment of lead poisoning but that prophylactic use of chelation therapy was contraindicated for several reasons. Included in these concerns was the possibility of increased lead absorption from

the gastrointestinal tract, an unsatisfactory response in reducing the body load of metabolically active lead, development of symptomatic lead poisoning among some workers receiving prophylactic chelation therapy and adverse effects of chelation therapy upon the metabolism of other trace metals besides lead and upon metal dependent enzyme activity. In addition there was concern that certain chelating agents had the potential to cause kidney damage and blood abnormalities.

Selikoff et al[25] reported preliminary data from a study of workers employed at two secondary smelters in the Indianapolis area. Approximately 150 workers exposed to lead were examined. Based upon results from blood lead analyses, about 30 percent were found to have blood lead levels in the range of 80 to 100 ug/100 and most workers had blood lead values of 60 ug/100g or greater. Blood lead levels in controls exposed to moderate levels of lead in a well controlled can factory were not elevated.

Approximately half of the workers studied had received at least one course of chelation therapy. Evidence of neurologic damage based either upon weakness of extensor muscles in the hands or a history of neurologic damage was found in approximately one quarter of workers studied. Neurologic damage became evident as early as 2-3 years following onset of lead exposure. About one quarter of the workers studied had a history of lead colic; many had more than one

episode. Eight workers had been hospitalized for lead poisoning. ZPP (zinc protoporphyrin) levels among these workers were extraordinarily elevated with values well in excess of 500 ug/100 ml reported. While blood lead levels generally remained under 100ug/100g as a result of chelation, ZPP's appeared to remain elevated despite chelation. Approximately half of the workers studied had evidence of mild or moderately severe anemia based upon hemoglobin determinations. Nerve conduction velocities indicated prolonged conduction times which could not be explained by age and suggested that lead may accelerate aging in the nervous system. These preliminary data indicated that although chelation therapy reduced blood lead levels there was evidence that chelation does not protect against the progression of neurologic damage or against metabolic and other effects caused by lead.

Summary Discussion

Shown in Table 1 is a summary of the beneficial as well as the adverse effects associated with chelation therapy. Chelating agents are generally effective in lowering blood lead levels and are indicated in the therapy of acute lead intoxication. However, the data presented above raise serious questions as to the safety of prophylactic chelation therapy particularly under conditions of continued lead exposure. Prophylactic chelation is defined both as the routine use of chelating or similarly acting drugs to prevent elevated blood lead levels in workers who are occupationally exposed to lead or as the use of these drugs to routinely lower blood lead levels to predesignated concentrations believed to be "safe." While use of chelating agents are justified in acute lead intoxication, particularly in children, evidence does not exist to justify their use on a prophylactic basis. The potential for chronic administration of chelating agents to cause kidney damage is a special concern. Adverse effects from chelating agents have been observed following both oral and intravenous administration. Both $CaNa_2$ EDTA and penicillamine have the potential to cause harm. The prevailing medical opinion is strongly opposed to the use of chelating agents on a prophylactic basis. Whenever chelating agents are used there is a need for close medical supervision including careful evaluation of renal function. Death and severe injury during and following use of chelating agents have been reported in the medical

literature. Prophylactic administration of $CaNa_2$ EDTA by whatever route under conditions of continued lead exposure is judged to be particularly hazardous. Use of chelating agents is not an adequate substitute for engineering controls and proper industrial hygiene practices. Both lead and $CaNa_2$ EDTA in sufficient dosages are established to be toxic to the kidneys. Prophylactic chelation may decrease the ability of the kidneys to protect themselves against the toxic effects of lead. A recent mortality study of workers exposed to lead conducted by Cooper and Gaffey,[26] for example, demonstrated an increase in deaths from end stage renal disease. In conclusion, prophylactic use of chelation to control lead absorption represents an unacceptable medical practice that cannot be condoned.

Summary

Chelating agents are useful in the therapy of acute overexposure to lead. However, prophylactic use of chelating agents, particularly under conditions of continued exposure to lead can be harmful to health. Potential adverse effects include kidney damage, symptomatic lead poisoning, increased absorption of lead from the gastrointestinal tract and disruption in the metabolism of trace metals other than lead. Prophylactic chelation is an unacceptable medical practice which cannot be condoned.

Table 1

Summary of the Beneficial as well as the Adverse Effects Associated with Chelation Therapy in Man

| Category | Observed Effect | References |
|---|---|---|
| Beneficial | Increased excretion of lead from the body and/or reduction in blood lead levels | 1,2,3,6,7,8, 10,14 |
| | Decrease in symptoms following treatment | 2,3,5,6,8,13, 14,24 |
| | Generally tolerated therapy well | 5,8,9 |
| | Advocate of prophylactic chelation | 9,12 |
| Adverse | Symptoms observed during therapy in at least some workers | 1,8,9,24 |
| | Increased absorption of lead from the gastrointestinal tract | 1,5,8,11,24 |
| | Imbalance in metabolism of metals other than lead | 2,4,24 |
| | Electrocardiographic changes | 3,20 |
| | Return of symptoms following chelation | 5 |
| | Elevated blood lead level following treatment | 6,8,10,14 |
| | Therapy associated with kidney damage | 9,10,11,16, 17,19,20,21, 22,23,24 |
| | Neurologic, hematologic or other damage associated with long term therapy particularly under conditions of continued lead exposure | 12,25 |
| | Therapy associated with severe neurologic damage | 11 |
| | Death Associated with Therapy | 8,16 |
| | Warning against prophylactic use | 4,5,10,13,14, 16,24 |

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