

Chelating Agents and Cadmium Toxicity: Problems and Prospects

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Symptoms and signs in humans after excessive exposure to cadmium usually involve the gastrointestinal tract after single oral intake, the lung after acute inhalation, and the kidney after long-term exposure. These organs are usually considered to be the "critical" organs, i.e., the organs most sensitive at a certain type of exposure. The type of Cd-related damage that is most common in humans is probably the renal toxicity after long-term exposure. Most animal experiments, including the most recently published ones, have involved study of gross toxicity and tissue distribution after injection of cadmium in acute experiments. The observations in the older literature that the influence of chelating agents on Cd distribution and excretion is confined to the early period after acute Cd exposure has been confirmed and extended, and the relationship to the time course of metallothionein synthesis has been demonstrated. Although the injection experiments concerning cadmium distribution, particularly those employing repeated exposure, may furnish information that can form a basis for speculation about long-term toxicity to the kidney, there is a lack of direct studies in animals of possible beneficial effects of chelating agents on renal toxicity of cadmium after prolonged exposure. Among the few studies reported, either an increased renal toxicity or a lack of influence on renal toxicity has been observed. The problems in finding a treatment scheme that can be beneficial for the renal toxicity resulting from long-term cadmium exposure thus remain; however, the prospects of finding such schemes in the future seem favorable in view of some of the recent observations.

Introduction

The toxicology of cadmium has attracted considerable interest during a number of years because of the cumulative properties of this element and the identification of its potential health impacts, particularly those related to long-term accumulation and subsequent damage to the kidney. The kidney is considered to be the organ that is most sensitive to long-term exposure to cadmium, i.e., the critical organ for this type of exposure. Although this type of cadmium-induced damage does not frequently occur in the general population, a high incidence has been reported in some population groups in areas where food and drinking water have been contaminated with cadmium. Also, among industrial workers (1) who have been exposed to cadmium for long periods of time, renal dysfunction may occur. Early stages of such renal dysfunction are not associated with any serious clinical complaints, except possibly a

higher incidence of renal stones.

The management of such cases usually does not require the use of drugs, but only removal of further exposure. Major clinical symptoms of renal disease are usually not seen. However, since the renal tubular dysfunction usually persists for many years, it would be desirable to have access to possibilities to treat this dysfunction. A safe drug without side effects would be required for that purpose. However, efforts made in the 1940s and 1950s to find such a drug were disappointing, and it has been customary not to advocate treatment of these types of cases. In the present paper the more important features of cadmium poisoning will be given, and the current evidence concerning influence of chelating agents on cadmium turnover and toxicity will be discussed.

Features of Cadmium Poisoning in Man and Experimental Animals

After a single injection (intravenously or intraperitoneally) of soluble cadmium salts into exper-

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imental animals, a number of lesions in various organs may occur (1). At sufficiently high doses, liver necrosis, necrosis of sensory ganglia and testicular necrosis (in male animals) or placental necrosis (in pregnant animals) is observed. Lethal effects are related to the liver necrosis, but testicular necrosis, for example, can be induced at considerably lower injected doses that do not give rise to damage to other organs. The testicles thus are to be regarded as the critical organ (in pregnant animals, probably the placenta). However, in acute toxicity experiments, where only mortality is recorded, the effects of cadmium on the liver may be the most important effect.

After short-term oral exposure, the type of damage that will be induced is to some extent dependent on the animal species. Whereas the vomiting reflex is quickly induced in humans at relatively limited concentrations of cadmium in ingested food or drink (about 15 mg/L), rats, for example, may tolerate much larger concentrations without such gastrointestinal reactions. In the latter species, therefore, both liver necrosis and other lesions may be observed after such exposure, whereas the gastrointestinal reactions are dominant in man. The gastrointestinal effect can be regarded as the critical effect in acute oral exposures.

After short-term inhalation, the lung damage is predominant; the lung may be regarded as the critical organ.

As discussed previously, long-term exposure to cadmium gives rise primarily to renal tubular proteinuria regardless of whether exposure is oral, by inhalation or by means of repeated long-term injection. However, lung damage may also occur in the long-term inhalation situation, i.e., when sufficiently high concentrations of cadmium are inhaled. When lower concentrations are inhaled during longer periods of times, lung damage is less prominent, and renal tubular proteinuria dominates. Recently it has been demonstrated in animals that even rather low concentrations of cadmium in air may give rise to lung cancer (2). However, usually the kidneys are considered as the critical organ. The lung cancer might well turn out to be the critical effect, in future evaluations.

Cadmium Chelation by Metallothionein

Cadmium chelation by metallothionein and its relationship to cadmium toxicity was originally suggested by Piscator (3) and Nordberg (4,5) and further reviewed by Andersen (6). A few general

aspects will be mentioned here. The deleterious effects of cadmium are due to binding at the sensitive site in the cell, i.e., metallothionein-cadmium or other types of cadmium chelates would be considered inactive. However, metallothionein-cadmium and chelate cadmium undergo breakdown in the tissues, and nonchelated cadmium may be released. When the tissue concentration of nonchelated cadmium exceeds a certain level, toxicity occurs in the tissue. This is important to remember when discussing effects of chelating agents on cadmium toxicity.

Chelating Agents and Cadmium Toxicity

This review will not attempt to be complete but will take up some of the more important evidence available concerning effects of chelating agents on cadmium toxicity. In 1946, Gilman et al. (7) documented a decrease in the acute mortality normally incurred after a single injection of cadmium when rabbits were treated with 2,3-dimercaptopropanol (BAL). However, several of the rabbits succumbed later from kidney damage. In a follow-up of these studies, Tepperman (8) showed that BAL increased the uptake of cadmium in the kidneys, an observation confirmed by Niemeier (9). Also, EDTA has been shown to decrease the acute lethality from a single injection of cadmium (10-13). However, EDTA has also been demonstrated to increase the nephrotoxicity of cadmium after repeated exposure in rabbits (10). Dalhamn and Friberg (14) presented evidence that a similar unfavorable effect of BAL upon cadmium toxicity can be observed during prolonged exposure. Tobias et al. (15) showed that prophylactic treatment with BAL had a deleterious effect upon mice exposed to cadmium chloride dust by inhalation. However, when BAL was given promptly after exposure to the cadmium dust, in an optimal course of repeated injections, it could reduce the mortality considerably. Also, BAL increased the cadmium content of the kidneys, but this seems not to have been of importance for mortality or pathological changes, as no renal pathology was observed following BAL treatment of mice poisoned by inhaling cadmium. The experiments by Tobias et al. were performed with an aerosol of CdCl_2 , an exposure situation less common in practice than exposure to CdO aerosol (cadmium fume). This latter exposure type was used in experiments by MacFarland (16), who showed that BAL treatment after exposure could considerably reduce the mortality. That chelating agents such as hydroxyethylene-

diaminetriacetic acid (HEDTA) and diethylenetriaminepentaacetic acid (DTPA) had a preventive effect upon acute cadmium toxicity and that they decreased the uptake of cadmium in the kidneys was reported by Eybl, Sykora and Mertl (11). Similar observations were made by Chatilena and Klaassen (12).

A decreased effectiveness of chelation therapy with time after a single injection of cadmium was observed by the early authors in the 1940s and 1950s, and these observations have been confirmed by recent investigations (13). Recent investigations led to an explanation for this phenomenon involving the induction of metallothionein synthesis which has been studied and discussed in relation to the binding to chelating agents (13,16). Strong intracellular binding of cadmium to metallothionein prevents most chelating agents from removing it from this natural chelate. In the *in vivo* chelation of cadmium with BAL and DTPA from rats exposed to cadmium, considerable decreases in tissue cadmium concentration were achieved both in the liver and the kidney in relation to untreated controls. In the animals treated with BAL only, most of the cadmium was excreted in the feces; this has been related to an increased biliary excretion of cadmium (16).

Chelating agents that are used in detergents have been investigated in relation to cadmium toxicity. Both nitrilotriacetic acid (NTA) and sodium tripolyphosphate (STPP) increase the acute toxicity of cadmium after subcutaneous injection (17,18) but have no effect on renal long-term toxicity of cadmium by the oral route in mice (17,19).

One problem with many of the recent studies is that the possibility of kidney damage was not investigated.

Cadmium Toxicity and the Influence of Some Chelating Agents

Basic Flow Scheme of Cadmium

As discussed by Nordberg (20) and Kägi (21) at this conference, cadmium is present as cadmium-albumin in blood; immediately after exposure, such cadmium will be taken up preferably by the liver (Fig. 1). During the first hours after uptake, cadmium in the liver will not be bound to metallothionein. The synthesis of metallothionein, however, will be induced, and after 24 hr, cadmium will mainly be bound to metallothionein. Cadmium metallothionein will to a large extent

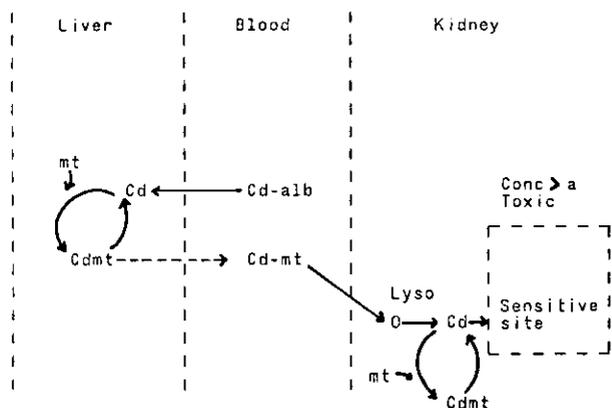


FIGURE 1. Scheme of flow of cadmium in the body demonstrating the role of binding forms in blood and metallothionein synthesis and degradation.

remain in the liver, but a small proportion will be released into the blood and another small proportion will be constantly turned over, whereby non-metallothionein-bound cadmium will be released, which will again induce synthesis of new metallothionein, and so on. Cadmium metallothionein that occurs in blood plasma will be quickly transported to the kidney, where it is filtered through the glomeruli and reabsorbed by the proximal renal tubule. The metallothionein moiety will be broken down by the lysosomes and nonmetallothionein-bound cadmium is released in the tissue. Such cadmium will stimulate renal metallothionein synthesis and there will be a constant turnover of metallothionein. A majority of renal cadmium will be bound to metallothionein in a long-term exposure situation; however, a certain amount of nonmetallothionein-bound cadmium will occur, and when this concentration exceeds a certain level at the sensitive sites in the cell, toxicity to the renal tubule will occur.

Influence on Acute Effects

It is important to consider the situation with metallothionein induction, particularly when discussing the long-term effects of cadmium. However, in the acute exposure situation (Fig. 2), metallothionein synthesis has not yet occurred, and the lethal effects of cadmium injection are related to liver toxicity. The increased toxicity of cadmium when injected subcutaneously in combination with STPP or NTA is related to a quicker uptake in blood and a higher level of cadmium-albumin in plasma which is quickly taken up by the liver. Thus, a high concentration of nonmetallothionein-bound cadmium is obtained in the liver before metallothionein synthesis has occurred. This leads to an increased liver toxicity.

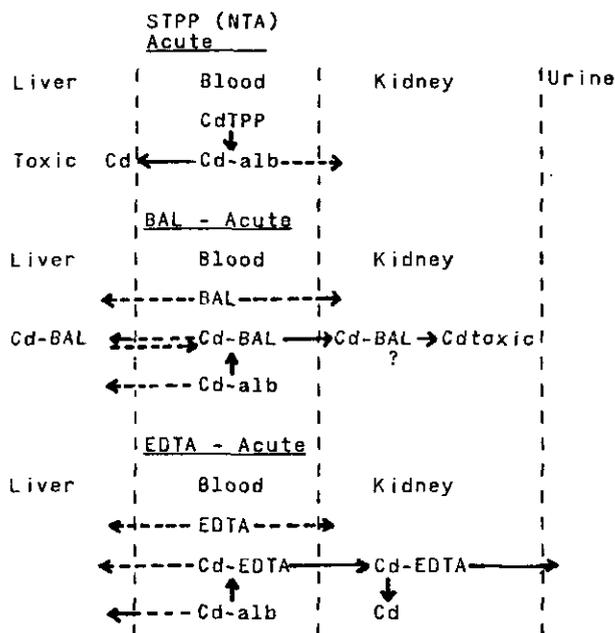


FIGURE 2. Scheme illustrating events of importance for acute cadmium toxicity when chelating agents are given simultaneously with cadmium.

The increased renal toxicity of cadmium when given in combination with BAL and the beneficial influence on effects related to other organs may be explained by the removal of cadmium from the cadmium-albumin complex in blood plasma and in tissues where the cadmium-BAL complex is formed instead. This Cd-BAL complex may displace Cd to other tissues than those at the site of uptake (e.g., lung), and a favorable effect in relation to effects on the uptake organ may be observed, whereas renal toxicity is a possible side effect of this type of chelation therapy.

The EDTA-cadmium complex also is stronger than the cadmium-albumin complex, and a removal from the albumin site to the EDTA complex will take place. The cadmium-EDTA complex will pass through the kidney into the urine. A small amount of cadmium will be released in the kidney, but toxic concentrations will not occur in acute cadmium poisoning, when relatively small amounts of cadmium are operating (in relation to the amounts involved in chronic renal cadmium damage). This explains the favorable effects of EDTA treatment in acute cadmium intoxication.

The situation with regard to long-term cadmium exposure is different due to the involvement of metallothionein, which, as has been discussed previously during this conference, is the most stable chelating agent internally formed in the body.

Influence of STPP on Chronic Cadmium Toxicity

When cadmium is combined with sodium triphosphosphate (STPP), cadmium triphosphate is formed, which quickly releases its cadmium to cadmium albumin in blood plasma (Fig. 3). An increased concentration of cadmium albumin will thus momentarily be formed, and a quicker uptake will occur in the liver. However, the total amount transferred will be approximately the same as without the chelating agent, and since the liver is not the critical organ in long-term exposure when relatively small amounts of non-metallothionein-bound cadmium are operating, toxic liver concentrations of nonmetallothionein-bound cadmium will not arise. Cadmium will be released in the same way from the liver to the kidney as without the chelating agent, and no effect on the renal toxicity should be expected. This is also what has been observed in actual long-term experiments.

Flow Scheme of Cadmium-BAL

When it comes to BAL, the cadmium-BAL complex, like BAL can move more freely through the cell membranes than cadmium-albumin (Fig. 4). The Cd-BAL complex also has been shown to be more readily excreted in bile than non-BAL-bound cadmium. Cadmium-BAL is probably more stable and more readily formed than cadmium-albumin, and BAL will thus probably displace cadmium from cadmium-albumin and thereby decrease the influx of cadmium into the liver but may increase the influx into the kidney. If sufficient amounts of BAL are not provided to the kidney at all times, the cadmium-BAL com-

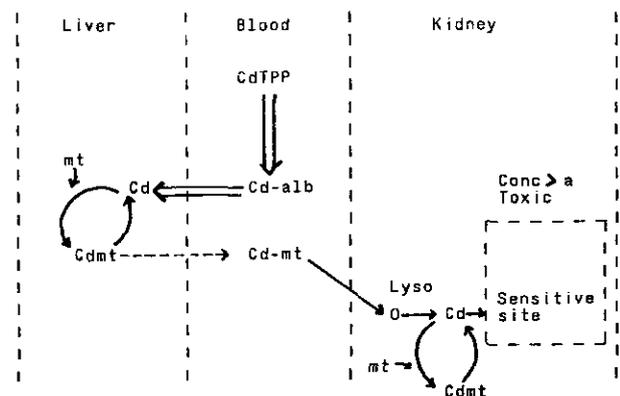


FIGURE 3. Scheme illustrating events taking place when cadmium and STPP are given in a long-term exposure situation.

plex may be broken down and add to the nonmetallothionein-bound cadmium in the kidney. If a borderline amount of this type of cadmium is already present in the kidney, the cadmium released from BAL may elevate the concentration above the critical concentration, and kidney damage may occur. This mechanism, which admittedly is somewhat hypothetical, would fit with observations of an increased renal toxicity when cadmium is given together with BAL in repeated injections. However, if cadmium-albumin is not present in plasma in any appreciable amount, BAL may have a beneficial effect in providing a means for increased excretion of cadmium from the liver. The effects of BAL would thus to a large extent be dependent on whether ongoing exposure to cadmium or mobilization of cadmium from absorption sites like the lung is taking place. When this is not the case, it may be that beneficial effects of BAL can be expected. However, this should be demonstrated in experiments where kidney damage has been induced. No such experiments have been published as yet.

Flow Scheme of Cadmium-EDTA

The cadmium-EDTA complex may be excreted more readily in the urine and thus EDTA injection may decrease renal concentrations of cadmium (Fig. 5). However, an increased renal toxicity may still be possible if EDTA is not provided in sufficient amounts at all times to keep up the cadmium-EDTA complex, so that no cadmium is released in the kidney from the cadmium-EDTA complex. If such release occurs, the already borderline toxic concentration of nonmetallothionein-bound cadmium that may be present in long-term cadmium exposure may be increased. The critical concentration for nonmetallothionein-bound cadmium may thus be exceeded, and renal toxicity may occur. An alternative explanation for such renal toxicity may be that cadmium-EDTA is more readily transferred to the sensitive sites where cadmium may be released from EDTA and bound to the sensitive receptor.

Summary

In summary, explanatory schemes concerning effects of cadmium in combination with acute and long-term toxicity have been presented as to accommodate as far as possible the published observations concerning such effects. It is important in the future that additional experimental research be made as to confirm or reject the hypothetical schemes proposed here. Particularly the possibility of a beneficial effect of chelation therapy on

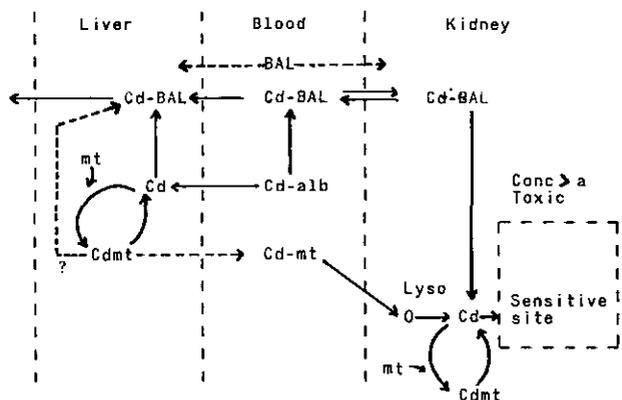


FIGURE 4. Scheme illustrating the flow of cadmium when BAL is given in repeatedly cadmium-exposed animals or humans.

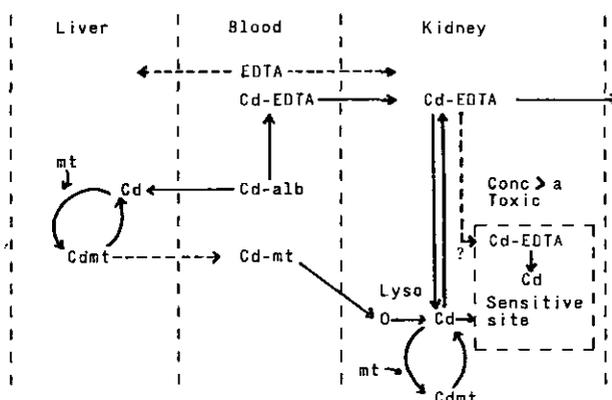


FIGURE 5. Scheme illustrating the flow of cadmium when EDTA is given to animals (or humans) repeatedly exposed to cadmium.

renal toxicity needs experimental confirmation. No firm predictions with regard to the possibility for such chelation therapy can be made at the present time even if long-term treatment with BAL and DTPA has shown favorable influence on organ concentrations of cadmium.

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