Evaluation of the Potential Role of Chelation Therapy in Treatment of Low to Moderate Lead Exposures

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In the overall long-term management of lead poisoning, chelation therapy can have short-term benefits; however, these benefits must be accompanied by drastic reduction in environmental exposure to lead if therapy is to have any long-term benefit. This discussion is limited to calcium disodium ethylenediaminetetraacetate (CaNa₂EDTA), the chelating agent that has been the mainstay of treatment of lead poisoning for the past 38 years, and to meso-2,3-dimercaptosuccinic acid (DMSA), a new and promising oral chelating agent, which is an orphan drug and is currently classified as an investigational new drug by the U.S. Food and Drug Administration. With both drugs, multiple courses of treatment will be needed if any substantial reduction in body lead burden is to be achieved. A major limitation of CaNa₂EDTA is the enormous diuresis of zinc that it produces. DMSA produces a comparable diuresis of lead, a greater decrease in blood lead, and has negligible influence on the urinary losses of zinc, copper, iron, and calcium. Limited experience to date in man has revealed no significant adverse side effects of DMSA. In animals, DMSA will promptly reduce the concentration of lead in brain and kidney, in particular. By contrast, similar 5-day courses of CaNa₂EDTA do not produce any net reduction in brain lead. This is important, as the brain is the critical organ of the adverse effects of lead in children. If the efficacy of DMSA is to be comprehensively evaluated ethically in children, new and more sensitive neurochemical, electrophysiologic, or other markers must be developed.

Introduction

Chelation therapy serves as a useful adjunct in the overall management of lead toxicity. However, its full potential can only be realized if it is coordinated with prompt and substantial reduction in environmental exposure to lead. The major agents that have been used for over 35 years are calcium disodium ethylenediaminetetraacetate (CaNa₂EDTA) and 2,3-dimercapro-1-propanol (BAL). Although it is still considered an investigational drug by the United States Food and Drug Administration (FDA) when used to treat lead poisoning, D-penicillamine (PCA), which can be given orally, continues to be used primarily as a secondary or maintenance drug. PCA is not highly effective and must be used with great caution because it is associated with a variety of adverse side effects, some of which, although rare, are potentially very serious (erythema multiformi, Stevens-Johnson syndrome, hemolytic-uremic syndrome). There is no doubt that chelation therapy can dramatically reduce the mortality of acute lead encephalopathy and reverse the clinical and biochemical effects of acutely symptomatic lead poisoning. During the prechelation therapy days, the mortality of severe acute encephalopathy was 66% (1). Today, with combined BAL-CaNa₂EDTA therapy, the mortality is probably no more than 1 to 2% (2). The rapidity with which the diagnosis is made probably is the critical factor. Even so, it is not clear that chelation therapy ameliorates to any significant degree the sequellae of the severe forms of the disease (3).

What, then, is the role of chelation therapy in the treatment of asymptomatic children with low to moderate increases in body lead burden? This discussion will be limited to CaNa₂EDTA, the principal drug used to treat lead toxicity for the past 38 years, and to meso-2,3-dimercaptosuccinic acid (DMSA), a most promising new oral chelating agent, which is an orphan drug and is currently classified by the FDA as an investigational new drug. Although limited and sometimes conflicting, experimental data suggest that supplementation with zinc, large oral doses of ascorbic acid, or thiamine given by injection may potentiate the beneficial effects of either CaNa₂EDTA or DMSA (4-6); these will not be discussed. A recent pilot study in children indicates that 2,3-dimercaptopropane-1-sulfonate (DMPS) may significantly increase the urinary loss of copper and is inferior to both CaNa₂EDTA (7) and DMSA in terms of the reduction in blood lead concentration (PbB) and the diuresis of lead induced. Furthermore, dermatological reactions, including at least one case of Stevens-Johnson syndrome, have recently occurred in patients receiving the drug for more than 5 successive days, so DMPS does not merit further consideration.

CaNa₂EDTA: Human Studies

It has been standard clinical practice for a number of years to administer CaNa₂EDTA parenterally for 5 days. Following

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a 2- to 4-day rest period, a second 5-day course may be administered. Limitation of courses to 5 successive days is based upon clinical experience in the 1950s, which showed that longer periods of continuous administration at higher doses than used today were nephrotoxic and were sometimes associated with fatalities due to renal failure (8).

Figure 1 shows changes in PbB concentration in a child in relation to intermittent 5-day courses of CaNa2EDTA. These data are probably representative of the way in which the drug is widely used in children in the U.S. today. The child is treated for 5 days, sent home, and recalled in a month or so, perhaps treated again, and so on. In this particular case, the physicians treating the child became frustrated and referred the child to me for more intensive chelation therapy. We are fortunate in Baltimore to have two pediatric intermediate care facilities in which children can be kept for treatment for longer periods of time than they can in general hospitals. Because of experimental evidence that CaNa2EDTA and PCA may increase absorption and retention of any lead in the gut, it is prudent to administer these drugs in a clean environment (9). As the exposure to lead in deteriorated paint had finally been corrected, the house was vacuumed thoroughly with a high efficiency particle accumulator (HEPA) vacuum, whereupon the child was discharged (Fig. 1). An example of serial changes in PbB in a child receiving intensive chelation therapy initially are shown in Figure 2.

Other changes that are uniformly associated with 5-day courses of CaNa2EDTA are summarized in Table 1. PbB concentration decreases to 55 to 60% of the pretreatment value at the end of the 5-day course, but within 4 days rebounds in hospital by an average of 5 μg lead/dL in this particular group.1 Serum zinc decreases within 48 hr to 70% of the pretreatment value, but rebounds within 3 to 4 days after of treatment as shown in Table 1 on day 9. Alkaline phosphatase, a zinc-dependent enzyme, decreases significantly, but quickly rebounds to the pretreatment value. Likewise, serum transaminases increase, but return to the pretreatment value within 3 to 4 days after treatment. The decrease in serum zinc is associated with the 17- to 20-fold increase in urinary loss of zinc. In the absence of therapy, young children excrete an average of about 200 μg zinc/day or 1 mg/5 days in urine. During 5-day courses of CaNa2EDTA, we have observed losses in children of 12 to 30 mg of zinc (10) and losses in adults of 60 to 100 mg of zinc in urine in 5 days. CaNa2EDTA, a nonspecific metal binding agent, also is associated with increases in the urinary losses of iron, manganese, copper, and cadmium. The losses of these other metals are small. It is probable that much of the toxicity of CaNa2EDTA is associated with the mobilization of zinc.

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1These studies were approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions. Prior informed written parental consent was obtained.

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**Figure 1.** Changes in PbB concentration in relation to intermittent 5-day courses of CaNa2EDTA. Serial changes in PbB (mg/dL) in a 25-month-old child are plotted on the ordinate against time (days) over a period of 17 months on the abscissa. Solid lines show changes during chelation therapy; the dashed lines show changes while not receiving therapy. Dosage of CaNa2EDTA (with added procaine, 0.5% final concentration) was 1000 mg/m2/24 hr given in divided dose every 12 hr by deep intramuscular injection for 5 days. The post-treatment PbB concentrations within 24 hr after the first three courses were 57, 58, and 58%, respectively, of the pretreatment values as shown at the left of the figure. Twelve months after the first course, the child received two courses of CaNa2EDTA in the same dosage separated by 4 days with the result that PbB decreased from 60 to 28 mg/dL. The child received oral PCA daily (500 mg/m2/dose) supplemented by CaNa2EDTA IM (500 mg/m2/dose) given on alternate days, which sustained the improvement. Rebound in PbB peaked 2 months later and then decreased spontaneously. Free erythrocyte protoporphyrin concentrations (not shown) decreased steadily throughout the 17-month period of observation.
The cumulative excretion of lead in urine is essentially linear in each child during the 5 days of therapy, although total output varies widely (12). The portion of the body burden of lead, which is available for chelation by CaNa$_2$EDTA, can be estimated by compartmental analysis as described by Piotrowski (11). In this procedure, linear regression analysis of log-transformed data on daily urinary excretion of lead during therapy is used to estimate the halftime and rate constant ($k$) for each child. $A_p$ is the total amount of lead excreted in urine during a 5-day course of therapy. These data can then be used to calculate the size of the prechelation lead pool ($A_o$), according to the formula $A_o = A_p/(1-e^{-kt})$. This procedure assumes a one-compartment, open model, which probably underestimates the pool, as there may be transfers of lead between pools during the 5 days. Furthermore, the kinetic studies of Rabinowitz et al. (12) indicate that a more complex model is required for lead.

Table 2 summarizes data for 18 preschool-aged children in whom we have obtained essentially complete 5-day collections of urine. In this group, mean pretreatment blood lead was 55 µg lead/dL whole blood, while the mean post-treatment PbB obtained 12 hr after the last dose of CaNa$_2$EDTA was 33 µg lead/dL, or 60% of the pretreatment level. Compartmental analysis revealed a wide range in the estimated pretreatment chelatable lead pools ($A_o$), while on average, 62% of the estimated pool was excreted during the 5-day course. In theory, one would want a chelating agent specific for lead that could be safely administered until the diuresis of lead terminated. This is not possible with CaNa$_2$EDTA for reasons of safety. Also, the data help to explain the rebound in PbB immediately after treatment, which presumably is due to internal redistribution of lead. Even after multiple courses of CaNa$_2$EDTA, body lead stores are likely to remain elevated (13).

**Table 1.** Changes in mean blood lead, serum zinc, serum transaminases,* and serum alkaline phosphatase during and after 5-day course of CaNa$_2$ EDTA in 10 children.

| Parameter                     | Day 0 | 2   | 5   | 9   |
|-------------------------------|-------|-----|-----|-----|
| Blood lead, mcg/dL            | 49.75 | —   | 26.55 | 31.25 |
| Serum zinc, mcg/dL            | 87.0  | 61.0 | 62.0 | 110.0 |
| ALT, U/L                      | 25.7  | —   | 43.4 | 28.0 |
| AST, U/L                      | 35.6  | —   | 59.0 | 32.2 |
| Alkaline phosphatase, U/L     | 272.0 | —   | 185.0 | 260.0 |

*Serum transaminases: ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase.

**DMSA: Human Studies**

DMSA was first synthesized by Friedheim and DaSilva in 1954. The antimony chelate of DMSA was initially used for the treatment of schistosomiasis (14). The Chinese first reported the use of DMSA as an antidote for poisoning due...
Table 2. Estimates of prechelation lead pool by compartmental analysis in 18 children treated 5 days with CaNa2EDTA.

| Patient number | Pretreatment PbB, mcg/dL | Compartamental analysis, mcg lead | A0 | A1 | A1 as % of A0 |
|----------------|--------------------------|----------------------------------|-----|----|---------------|
| 1              | 52                       | 4678                             | 2490| 53 |               |
| 2              | 51                       | 3124                             | 1720| 55 |               |
| 3              | 70                       | 2346                             | 1710| 73 |               |
| 4              | 42                       | 1858                             | 1230| 66 |               |
| 5              | 46                       | 1345                             | 850 | 53 |               |
| 6              | 60                       | 4840                             | 3610| 75 |               |
| 7              | 54                       | 1817                             | 1760| 97 |               |
| 8              | 53                       | 1799                             | 1770| 98 |               |
| 9              | 97                       | 4988                             | 3150| 63 |               |
| 10             | 41                       | 2568                             | 1700| 66 |               |
| 11             | 47                       | 1954                             | 826 | 42 |               |
| 12             | 60                       | 5136                             | 2172| 42 |               |
| 13             | 59                       | 3974                             | 2003| 50 |               |
| 14             | 37                       | 5165                             | 2185| 42 |               |
| 15             | 56                       | 4056                             | 1825| 45 |               |
| 16             | 49                       | 2064                             | 1410| 68 |               |
| 17             | 48                       | 2307                             | 1454| 63 |               |
| 18             | 52                       | 2126                             | 1218| 57 |               |

Table 3. Estimates of prechelation lead pool by compartmental analysis during first 5 days of oral DMSA therapy.

| Patient number | Pretreatment PbB, mcg/dL | Compartamental analysis, mcg lead | A0 | A1 | A1 as % of A0 |
|----------------|--------------------------|----------------------------------|-----|----|---------------|
| 1              | 43                       | 1678                             | 844 | 51 |               |
| 2              | 42                       | 1450                             | 855 | 59 |               |
| 3              | 70                       | 6237                             | 4057| 65 |               |
| 4              | 60                       | 5636                             | 3657| 65 |               |


dosage of CaNa2EDTA = 1000 mg/m² day in divided dose every 12 hr, intramuscular.

calculations: \( A_0 = (A_1/1 - e^{-k \cdot t}) \) where \( A_0 \) = prechelation lead pool, \( A_1 \) = total lead excreted in 5 days, and \( k \) = rate constant.

Compartmental analysis of the data (Table 3) tentatively suggests that the percentage of the estimated prechelation lead pool excreted in 5 days is similar to that observed with CaNa2EDTA. This, of course, is not to say that the pools of lead available for chelation by CaNa2EDTA and DMSA are identical, although this very limited data base suggests that they may be of comparable magnitude. At the present time, studies are in progress in various centers to determine whether longer courses of DMSA may be both safe and more efficacious than 5-day courses.

Figure 4 shows serial blood lead data in four children who have received five 10-day courses of oral DMSA in the Pediatric Clinical Research Unit of the Johns Hopkins Hospital. These studies were carried out on an in-patient basis to preclude the possibility of excessive ingestion of lead that might occur on an out-patient basis. During the first 5 days, all received 1050 mg DMSA/m²/day in three divided doses. During the second five days, dosage was reduced to 350 mg DMSA/m² day given in divided dose. Increase in PbB within a few days after treatment is observed in all; however, more importantly, those with pretreatment PbB concentrations of 52, 60, and 70 µg/dL show increasing blood lead concentration while on therapy during the second 5 days when the lower dose was given. The child with the initial pretreatment PbB of 70 µg received to mercury and lead (25). Within the past decade, substantial interest in DMSA as a promising oral chelating agent for the treatment of lead toxicity has developed. Its pharmacology has been reviewed by Aposhian (16) and Aaseth (17). DMSA has a substantially wider therapeutic index than other agents used to treat lead toxicity. Graziano et al. have given DMSA orally for 5 days to both adults (18) and children (19) and found that it is well tolerated; it reduces PbB to nearly 25 to 30% of the pretreatment value; it is associated with rapid reversal of the biochemical indicators of lead's adverse effects on heme synthesis; and it induces a diuresis of lead nearly comparable to that associated with administration of CaNa2EDTA. Efficacy is dose-related. Oral dosage of 30 µg/kg of body weight per day in adults or 1050 mg/m²/day in children given in divided dose is the most effective dose (Fig. 3). No significant increase in urinary loss of zinc, copper, iron, or calcium is observed. To date, the only changes noted in humans have been occasional and transient increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). As with CaNa2EDTA, blood lead concentration rather promptly rebounds immediately following treatment.

In our clinic, we have essentially complete 24-hr urine collections made on the Pediatric Clinical Research Unit of the Johns Hopkins Hospital in four children. Analysis of the data indicates that, as with CaNa2EDTA, the cumulative 5-day excretion of lead during treatment with DMSA is essentially linear with dose.1 The total amounts of lead excreted during 5 days (\( A_0 \)) are well within the range that has previously been observed in children with comparable pretreatment PbB concentrations who were treated with CaNa2EDTA in a dose of 1000 mg/m²/day given in divided dose every 12 hr by deep intramuscular injection (with added procaine).
ROLE OF CHELATION THERAPY IN TREATMENT OF LEAD EXPOSURES

**FIGURE 4.** Changes in PbB concentration during and after 10-day courses of oral DMSA therapy. PbB (mcg/dL) values are plotted on the ordinate against time (days) on the abscissa. The solid portion of each line shows changes in serial PbB concentration while on therapy in hospital; the dashed portion of each line shows post-treatment changes after discharge to dwellings thought not to contain lead paint hazards. Data are shown for four children, one of whom received a second 10-day course when PbB rebounded to 52 mcg/dL 2.5 weeks after the first course of therapy. During the first 5 days of treatment, DMSA was given orally in divided dose (1050 mg/m²/day) and then reduced to 350 mg/m²/day during days 6 to 10. Note that PbB increased during therapy when the dosage was reduced to 350 mg/m²/day in the children with pretreatment PbB concentrations of 70, 60, and 52 mcg/dL, respectively.

A second 10-day course of therapy when his PbB rebounded to 52 μg/dL whole blood within 2.5 weeks after the first course. It seems clear, then, that some adjustment in dosage will have to be made; indeed, Graziano (personal communication) has found that an initial 5-day regimen at 1050 mg/m²/day followed by reduction of dosage to 700 mg/m²/day will prevent a rise in PbB during an additional 2 weeks of therapy at this dose. It is clear, then, that repeated courses of oral DMSA will be needed in many if not all cases. The determining factor is probably the magnitude of the body lead burden prior to therapy.

Recent Experimental Studies

According to Aaseth (17), "Enhanced excretion induced by a drug is meaningless from a therapeutic point of view if it is not paralleled by a decrease of the metal concentration in the critical organ." Recent experimental and clinical studies provide compelling evidence that the developing brain is the critical organ for the toxic effects of lead in the fetus and young child (20). In the absence of a sensitive biological marker that could be ethically used in children to assess the effects of chelating agents on central nervous system function in young asymptomatic children with low to moderately increased body lead burdens, we must turn to experimental animals.

Recently, investigators have turned more and more to chronic, low-level lead exposure, which probably provides a better animal model than past studies in which acute treatment with high doses of lead followed by high doses of chelating agents were used. It has long been known that the administration of chelating agents poses the risk of translocation of metals from one tissue site to another and from one organ to another. For example, experimental administration of lead together with disulfiram not only results in much greater uptake of lead by brain than dosing with lead alone, but also intensifies the neurochemical disturbances attributable to lead (22).

Cory-Slechta et al. (22) have administered CaNa₂EDTA to chronically poisoned rats over a 5-day period, sacrificing animals for tissue analyses after 1, 2, 3, 4, or 5 days of drug administration. As in humans, decrease in PbB concentration and a brisk diuresis of lead were observed. On the other hand, liver lead increased for 3 days and then decreased. More importantly, particularly at the higher dose used, there was a sharp increase in the concentration of lead in brain after a single injection (Fig. 5). In agreement with the studies of Goyer and Cherrain (4) and Dhawan et al. (5), no net decrease in brain lead was observed after 5 days. Goldstein and colleagues (23) earlier found that the uptake and retention of lead by brain in immature rats was greater than in their mothers and that brain lead was not affected by EDTA.
In man, a sharp and significant increase in plasma lead, peaking 1.5 hr after injection of CaNa₂EDTA, has again been demonstrated recently (24). Araki et al. (25) also found in lead workers that the amount of lead excreted in urine under the influence of CaNa₂EDTA was significantly correlated with PbB and erythrocyte lead, but not with plasma lead. Taken together, these studies call for a reappraisal of the role of CaNa₂EDTA, particularly its diagnostic use (26).

Cory-Slechta (27) has also carried out a similar study administering DMSA by intraperitoneal injection to rats. Under these conditions, prompt reduction in brain lead was observed (Fig. 6) in agreement with the earlier report of Graziano et al. (28). Kidney lead was also substantially reduced. The limited experimental data do not provide a clear indication of the influence of DMSA on bone lead. Cory-Slechta (27) also analyzed the tissues of animals sacrificed 4 months after a 5-day course of DMSA and found that internal redistribution of lead had occurred and that the concentrations of lead in the various tissues did not differ significantly from those found in control animals (Fig. 7). Only Bankowska and Hine (6), who administered intermittent chelation therapy to mature rats over a 6-week period, have reported a significant reduction in brain lead in association with 6 weeks of treatment with either CaNa₂EDTA or DMSA.

**Efficacy of Chelation Therapy Alone**

The available clinical and experimental data indicate that oral therapy with DMSA is most promising for the treatment of low to moderate increases in body lead burden. Most importantly, studies in animals indicate that short courses of DMSA significantly reduce brain lead, while CaNa₂EDTA does not. DMSA may also be more effective in reducing kidney lead. It is, however, clear that long-term therapy will be required if possible long-term benefits are to be realized. The influence of DMSA on essential metals has not been extensively studied. Most of the experimental data are based on studies in mature rodents. Future studies employing immature rodents would be most helpful in delineating age-related differences in their responses to DMSA and its influence on the neurochemical and neurobehavioral effects of lead. Are there points at which some of these effects might be reversible by treatment with DMSA?

Of particular interest to clinicians is the report of Kapoor et al. (29). These workers administered DMSA orally to rats immediately following oral lead dosing and found that absorption and whole-body retention of lead was significantly reduced in comparison with controls. The possible enhancement of absorption and retention of lead has long been a serious clinical concern with regard to other chelating agents. Even so, these authors point out the technical difficulties
of such experiments and note that chelation is not a substitute for control of exposure to lead. A major limitation of CaNa₂EDTA is its ability to mobilize significant amounts of zinc (and possibly manganese). Limited data suggest that depletion of zinc can be blunted when ZnCaEDTA is given to rats. Whether this would prevent some of the other unwanted effects of CaNa₂EDTA is not known.

In comparison with CaNa₂EDTA, DMSA appears to produce a comparable diuresis of lead and a greater effect on PbB in humans. In children and adults increases in the urinary loss of zinc, copper, iron, and calcium with DMSA are quite small and probably clinically insignificant. With regard to CaNa₂EDTA, its practical disadvantage is the fact that it must be administered parenterally, and its biological disadvantage is the substantial reduction in plasma zinc and the enormous diuresis of zinc associated with its administration. It also causes statistically significant increases in the urinary losses of manganese and iron. For these reasons, it does not appear to be an ideal agent for the treatment of modest increases in body lead burden.

The possibility that DMSA might reduce brain lead in children, in particular, is intriguing. To assess this possibility, new and more sensitive neurochemical, electrophysiologic, or other biologic markers of central nervous system function are needed. At the present time, the most common markers of biologic effect of lead are those associated with heme synthesis. Clinical experience to date also indicates that early intervention before a very substantial increase in body lead burden has occurred is more likely to be associated with a favorable outcome.

Post-Treatment Lead Exposure

The potential benefits of even repeated courses of chela-
tion therapy will be largely vitiated unless post-treatment exposure to environmental lead is drastically reduced. From the practical point of view, particularly in regard to children exposed to lead primarily in old, deteriorated residential paint, reduction in exposure is not readily achieved. Figure 8 shows serial blood lead data for 184 children during the first 12 months following therapy in hospital (31). Children are grouped according to the type of housing to which they returned. All had a PbB ≥ 50 μg/dL prior to treatment and were treated for an average of 52 days in hospital. Those returning to or visiting old housing that had been abated according to local ordinances in Baltimore at the time showed average PbB of 38 μg/dL or greater. Only those discharged to public or gut-rehabilitated housing showed somewhat better, but still not acceptable, results, even 2 to 2.5 years after therapy. Again, given the newer evidence on the subtle, adverse effects of lead on mental development in children, a highly favorable outcome would not be expected. Newer and far more stringent regulations for the abatement of lead paint hazards have recently been introduced by the City of Baltimore and the State of Maryland. These regulations place greatest emphasis on reduction of interior household dust lead. It is hoped that these regulations, in combination with recent reductions in exposure to lead in air and food, may lead to a better outcome in coming decades.

Summary

In summary, DMSA is a most promising new oral chelating
agent for the treatment of low and moderate lead exposures. Early studies indicate that short courses are safe and efficacious. On the other hand, any substantial reduction in body lead burden will probably require administration of DMSA over a period of at least several months either continuously or intermittently. The safety and efficacy of long-term treatment require further study. Early intervention is likely to be much more efficacious than late intervention during the chronic phase of plumbism. New biologic markers will be needed to assess its efficacy with regard to the developing central nervous system in young children. For beneficial effects over the long run, drastic reduction in environmental exposure to lead is essential.

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