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Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning

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Summary

Background: Chelation therapy has been used as a means of reducing the body burden of lead for five decades. Intravenous sodium calcium edetate has been the preferred agent, but there is increasing evidence that dimercaptosuccinic acid (DMSA) is also a potent chelator of lead.

Methods: Oral DMSA 30 mg/kg/day was administered to adults with blood lead concentrations $\geqslant 50$ μg/dl. The impact of DMSA on urine lead excretion, on blood lead concentrations and on symptoms was observed. The incidence and severity of adverse effects was also recorded.

Results: Thirty-five courses were given to 17 patients. DMSA significantly ($P < 0.0001$) increased urine lead excretion and significantly ($P < 0.0001$) reduced blood lead concentrations. Mean daily urine lead excretion exceeded the pre-treatment value by a median of 12-fold with wide variation in response (IQR 8.9–14.8, 95% CI 10.1–14.6). Pre-treatment blood lead concentrations correlated well with 5-day urine lead excretion. Headache, lethargy and constipation improved or resolved in over half the patients within the first 2 days of chelation. DMSA was generally well tolerated, but one course was discontinued due to a severe mucocutaneous reaction. There was a transient increase in alanine aminotransferase (ALT) activity during 14% of chelations. DMSA caused a significant increase in urine copper ($P < 0.0001$) and zinc ($P < 0.05$) excretion.

Conclusion: Oral DMSA 30 mg/kg/day is an effective antidote for lead poisoning, though there is a wide inter- and intra-individual variation in response.

Background

Lead poisoning is one of the oldest diseases known to man and cases still occur from occupational exposure[1] and ingestion of lead-containing materials.[2] Lead has deleterious effects on all major body systems at blood concentrations $\leqslant 30$ μg/dl[3–5] and is particularly damaging to the developing nervous system.[6–8] Symptoms are particularly likely at blood lead concentrations $\geqslant 50$ μg/dl.[3,9] Chelation therapy has been used for over half a century as a means of reducing the body burden of lead. While no controlled clinical studies have been performed to confirm that chelation reverses the clinical, biochemical or physiological effects of lead, there are substantial data from observational studies to suggest improved outcome with chelation therapy.[10–22]

Intravenous sodium calcium edetate has been the mainstay for treatment of lead poisoning for over half a century. With evidence that the water-soluble derivative of dimercaprol, dimercaptosuccinic acid [the Recommended International Non-proprietary Name (rINN) of the *meso* form is succimer; DMSA is the shortened chemical name], is also a potent chelator of lead,[21–24] several countries, for example the USA, have approved DMSA as the standard of

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care for moderate lead poisoning. However, in other countries, sodium calcium edetate remains the preferred agent. Potential benefits of DMSA over intravenous sodium calcium edetate are that it may be administered orally and causes less zinc depletion than the parenteral antidote.[20]

It has been demonstrated that DMSA 30 mg/kg/day is significantly more effective than either 10 or 20 mg/kg/day both in terms of enhancing lead excretion and reducing blood lead concentrations.[21] The same study also showed that the typical rebound increase in blood lead concentration after DMSA therapy is largely complete within 1 week of the last dose. For these reasons, DMSA 30 mg/kg/day was administered to our patients and a break of at least 1 week was interposed between each course to allow time for redistribution of lead from bone to soft tissues and blood.

Few clinical studies[20,21,24] have involved daily urine and blood measurement of lead, so the impact of DMSA on the body burden of lead has not been characterized fully. Our objectives were to make a detailed assessment of the effect of oral DMSA 30 mg/kg/day on urine lead excretion, blood lead concentrations, symptoms attributable to lead poisoning and the incidence and severity of adverse effects, including depletion of essential trace metals.

Methods

Patients (⩾16 years) presenting with lead poisoning between January 1991 and April 2008, regardless of the source of exposure (occupational or ingestion of lead-containing traditional remedies), and who had a blood lead concentration ⩾50 μg/dl and who consented to receive treatment, were admitted to the West Midlands Poisons Unit (WMPU), City Hospital, Birmingham, UK. A value of 50 μg/dl was chosen on the basis that although the literature and clinical experience indicate that lead can cause subtle health effects in adults at concentrations <50 μg/dl, symptoms were more likely to occur at ⩾50 μg/dl. However, the presence of symptoms in addition to a blood lead concentration ⩾50 μg/dl was not an absolute requirement for inclusion since a blood lead concentration ⩾50 μg/dl is by itself evidence of lead poisoning. Admission not only facilitated urine and blood collection but also prevented the possibility of continued lead exposure. Patients were given more than one chelation course if the blood lead concentration at least 1 week after the initial course remained ⩾50 μg/dl and they consented to treatment. The only exclusion criterion was a previous confirmed or suspected adverse reaction to DMSA.

DMSA 30 mg/kg/day was administered as a series of courses each lasting for at least 5 consecutive days. The decision when to terminate a DMSA course after 5 days took into account resolution of symptoms, daily urine lead excretion and reduction in blood lead concentration. The course was stopped short of 5 days only if there was non-compliance or suspected adverse effects of treatment. A complete break of at least 1 week was interposed between courses to allow time for redistribution of lead from bone to soft tissues and blood.

Pre-treatment investigations included a 24-h urine collection for measurement of lead, copper and zinc excretion. Plasma creatinine concentrations, plasma alanine (ALT) or aspartate aminotransferase (AST) activities, serum zinc and copper concentrations and a full blood count were also assayed. Serial 24-h collections of urine were made during treatment for assessment of lead, zinc and copper excretion. To maximize compliance, patients were interviewed daily to confirm that no errors had occurred in urine collection. If urine had been lost for any reason, the collection was documented as failed for that day. Blood lead concentrations were measured daily and plasma zinc and copper concentrations were also monitored during each chelation course. Plasma creatinine concentrations, plasma ALT or AST activities and a full blood count were measured during treatment. Symptoms were recorded daily.

The results are reported to reflect the effect of each day's treatment. Thus, results reported as pre-chelation (baseline or Day 0) are those from samples taken in the 24 h before the first dose of chelation. Thereafter, blood or plasma concentrations are recorded at the end of the respective day's treatment. That is, 'Day 1' results are from samples drawn 24 h after the first dose, 'Day 2' from samples drawn 24 h after the second dose, etc. Similarly, urine metal excretion results are presented to reflect the impact of each dose so that 'Day 1' results are excretion data for the 24 h immediately following the first dose, etc.

Heavy metal analyses of blood, serum and urine were undertaken by the Regional Toxicology Laboratory at City Hospital, Birmingham, part of the Supraregional Assay Service (SAS) for heavy metals. Blood samples were immediately stored at 4°C, either as whole blood (for lead) or after spinning down and separating serum (for zinc and copper). Analyses were undertaken usually in real time and always within 1 week of collection. Urine collections were measured and an aliquot was saved at 4°C until assay (usually within 1 week) and then frozen as storage space allowed. Prior to

2004, blood and urine lead and urine copper concentrations were measured by graphite furnace atomic absorption spectrometry (GF-AAS), serum copper and zinc and urine zinc concentrations were measured by flame atomic absorption spectrometry (Flame-AAS). Thereafter, all analyses with the exception of those for blood lead were performed using inductively coupled plasma mass spectrometry (ICP-MS). Calibration was undertaken using matrix matching, that is, using the same medium, blood or urine, as that to be analysed. Analytical accuracy was checked against assigned samples distributed to all SAS laboratories as part of the approved quality control process. In addition, laboratory performance was monitored by participation in internationally recognized, accredited, external quality assurance schemes, three for blood lead and two for the remaining analytes. Biochemical and haematological parameters were analysed by the Department of Pathology, City Hospital, Birmingham.

Minitab™ statistical software (release 13) was used to analyse data. Data were tested for normality using the Kolmogorov–Smirnov test with $P < 0.05$ to indicate a non-normal distribution. If this was the case, pre- and post-treatment parameters were compared using the non-parametric Wilcoxon one sample test with significance at 5%. Where the Kolmogorov–Smirnov test for normality resulted in $P > 0.05$, data were treated as a normal distribution, using the paired *t*-test to compare differences before and after treatment with a 5% level for statistical significance. Correlation was measured using the Pearson product moment coefficient for normally distributed data and the Spearman correlation coefficient for data that were not normally distributed.

Results

All patients who presented to the West Midlands Poison's Unit with a blood lead concentration $\geqslant$50 μg/dl consented to treatment with DMSA, with the exception of one patient who had suffered an adverse reaction previously (see below) and who was treated with sodium calcium edetate. Thirty-five courses of oral DMSA were given to 17 patients. Patient ages ranged from 17 to 68 years (mean 45 years); of whom four were females. The mean ± SD of courses per patient was 2.1 ± 1.3. Twenty-two courses involved 11 individuals who had been taking lead-containing traditional remedies for between 3 weeks and 1 year for problems including eczema, diarrhoea, diabetes, hypertension and nocturnal enuresis. Ten courses were given to five patients who had been exposed to lead occupationally for several years. The source of exposure for one patient (three courses 33, 34 and 35) could not be determined.

Chelation therapy commenced within 24 h of completion of the pre-treatment urine collection in 33 cases and within 72 h in 1. On one further occasion, the baseline investigations were 6 days before DMSA as the patient was allowed home following the pre-chelation assessment. DMSA 30 mg/kg/day was administered as a single dose for 32 courses and in divided doses in three to achieve compliance. Thirty-two courses continued for at least 5 days and 12 of these continued beyond 5 days. The decision to continue chelation beyond 5 days was a clinical judgement based on the blood lead concentration, evidence that the daily urine lead excretion on Day 5 remained substantial and continuing symptoms. Three courses were discontinued before 5 days; two (01 and 02) due to poor compliance and the other (06) to the development of a mucocutaneous eruption.

Urine collections during two 5-day chelations (24,25) were incomplete due to lack of cooperation by the patient. Complete urine lead excretion data were available, therefore, for 30 5-day courses. Figure 1 illustrates the median, IQR and range of urine lead excretion and shows that the amount eliminated falls with successive days of treatment. In 26 of 30 courses of at least 5 days duration, urine lead excretion was maximal during the first day. Lead excretion on Day 1 expressed as the percentage of 5-day excretion varied between 23% and 46% (mean ± SD 30.7 ± 5.2, 95% CI 28.7–32.6%).

As paired data, there was a highly significant difference ($P < 0.0001$) in daily urine lead excretion before and during 5 days of DMSA. The median difference in daily urine lead excretion with chelation was 1329 μg/24 h (IQR 975–2918, 95% CI 1243–2675 μg/24 h). The factor by which mean daily urine lead excretion exceeded the pre-treatment value varied between 1.3 and 37.1 (median 12.0, IQR 8.9–14.8, 95% CI 10.1–14.6). This variation was observed not only between individuals but also in the same individual given repeated courses. In one patient, during the second course of chelation the urine lead excretion was only 1.3 times greater than the pre-chelation value. This is not easily explained but the possibility of contamination of the pre-chelation sample cannot be excluded.

Pre-treatment blood lead concentrations (Fig. 2) correlated well (Spearman rank correlation coefficient 0.81, $P < 0.0001$) with the total 5-day urine lead excretion for each course. The Spearman rank coefficients for pre-chelation urine lead excretion vs. 5-day urine lead excretion (Fig. 3) and for

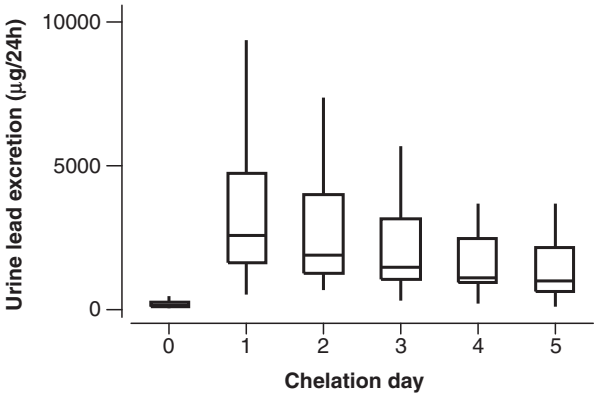

Figure 1. Median, IQR and range of daily urine lead excretion with DMSA for 30 courses of at least 5 days duration.

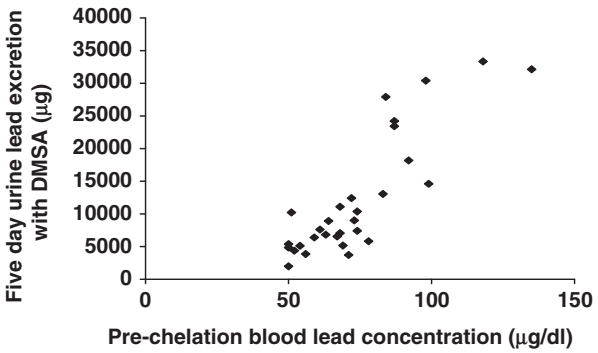

Figure 2. Scatter plot of pre-chelation blood lead concentration and urine lead excretion during 30 5-day courses of DMSA.

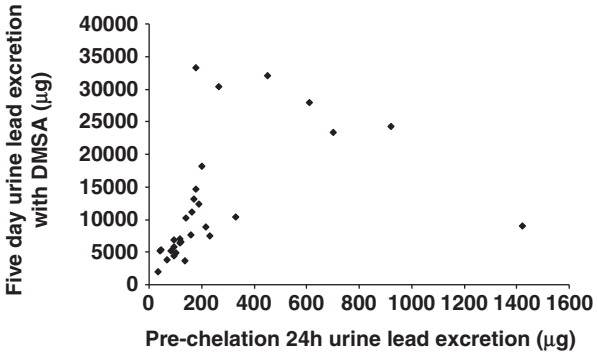

Figure 3. Scatter plot of pre-chelation 24 h urine lead excretion and urine lead excretion during 30 5-day courses of DMSA.

pre-treatment blood lead concentration vs. pre-treatment urine lead excretion (Fig. 4) ($n = 30$) were 0.82 ($P < 0.0001$) and 0.72 ($P < 0.0001$), respectively.

Blood lead data were available for 32 5-day courses of DMSA. Figure 5 shows that the median (with IQR and ranges) daily blood lead concentration fell fairly consistently with treatment. The

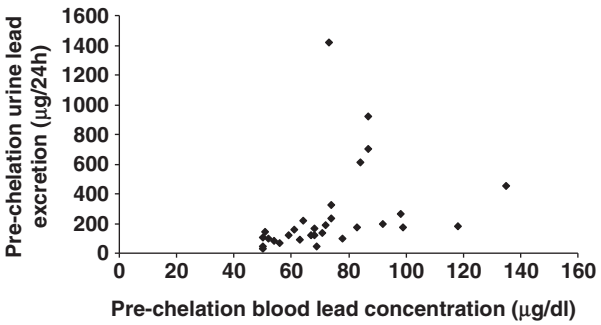

Figure 4. Scatter plot of pre-chelation blood lead concentration and pre-chelation urine lead excretion for 30 5-day courses of DMSA.

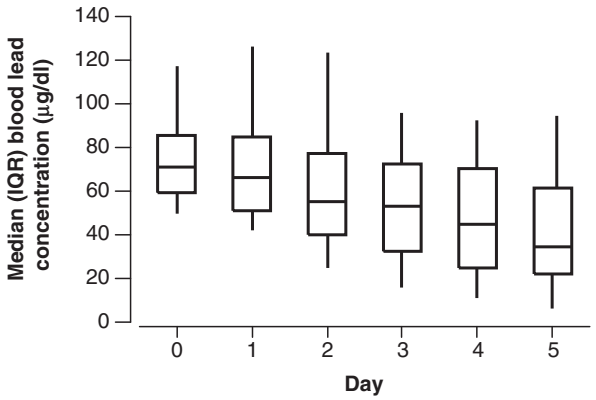

Figure 5. Median (IQR and range) blood lead concentrations with DMSA 30 mg/kg/day for 32 five day courses.

mean ± SD blood lead concentration after treatment was 42.8 ± 23.7 μg/dl, which was significantly ($P < 0.0001$) lower than the mean ± SD pre-chelation value of 74.2 ± 19.9 μg/dl (95% CI for the difference 25.7–37.4 μg/dl). The mean ± SD decline in blood lead concentration with chelation was to 55.4 ± 21.9% of the respective pre-treatment value (95% CI 47.2–63.5%).

Twelve courses of DMSA extended beyond 5 days though reliable urine data were available for only 11 of these. Table 1 summarizes the effect of chelation beyond 5 days on urine lead excretion and shows that whereas mean daily urine lead excretion during the first 5 days was between 5.3 and 37.1 (median 13.1, IQR 10.9–22.8) times pre-chelation values, it varied between 1.9 and 13.3 (median 7.6, IQR 3.0–9.9) times for additional days. Thus, lead elimination substantially higher than pre-chelation was achieved beyond 5 days in selected patients.

The effect on blood lead concentrations of prolonging treatment beyond 5 days is shown in Table 2. In most cases, where the concentration after 5 days remained >50% of the pre-chelation value, additional treatment led to a further reduction in the blood lead concentration. For one course (24),

Table 1 Effect of DMSA beyond 5 days on urine lead excretion

Course code	Further days treatment	24-h urine (Pb μg)				
		Pre-chelation	Mean of days 1–5	Mean of days 1–5/ pre-chelation	Mean of further days	Mean of further days/ pre-chelation
05	1	33	395	12.0	277	8.4
07	1	189	2483	13.1	1108	5.9
09	3	43	1030	23.9	574	13.3
12	4	200	3636	18.2	2358	11.8
13	4	920	4845	5.3	2775	3.0
15	3	612	5582	9.1	1800	2.9
16	1	84	1023	12.2	157	1.9
17	2	267	6081	22.8	2248	8.4
26	2	180	6669	37.1	1789	9.9
33	2	171	2611	15.3	1099	6.4
34	1	120	1312	10.9	911	7.6
Median (IQR)	2 (1–3.0)	180 (84–267)	2611 (1030–5582)	13.1 (10.9–22.8)	1108 (574–2248)	7.6 (3.0–9.9)

Table 2 Effect of DMSA beyond 5 days on blood lead concentration

Course code	Additional days treatment	Blood lead concentration as percentage of pre-chelation value				
		Day 5	Day 6	Day 7	Day 8	Day 9
05	1	44	40	–	–	–
07	1	47	46	–	–	–
09	3	36	33	30	26	–
12	4	73	82	75	65	48
13	4	67	62	61	53	51
15	3	62	54	54	54	–
16	1	48	[a]	–	–	–
17	2	66	69	60	–	–
24	3	102	98	91	[a]	–
26	2	52	48	39	–	–
33	2	93	83	82	–	–
34	1	79	67	–	–	–

[a]Patient left before blood taken.

the lead concentration was slightly higher after 5 days' chelation than before treatment. This is difficult to explain, but occurred in the individual in whom urine data were not analysed due to extremely poor compliance with sample collections. Failed compliance with treatment may have contributed or the patient may have continued surreptitiously taking the lead-containing traditional remedy that was the cause of poisoning.

The most commonly reported symptom was headache (in 14 of 35 cases). This improved in 11 patients by Day 2 of treatment, in one by Day 5 and remained unchanged in the remaining two. Lethargy, a presenting complaint in 14 patients, improved after two doses of DMSA in 11 cases and by the fifth dose in the remaining three. Seven of 10 patients reported improvement in constipation and in 6 of 7 abdominal pain resolved after 2 days chelation. Dizziness, complained of by four patients, resolved in one case before the first dose of DMSA was given and in two others by the second day of chelation. Other symptoms (impaired concentration, limb paraesthesiae, anorexia, nausea and vomiting) showed some resolution after 2 to 3 days' chelation with the exception of one of two patients who listed weight loss as a presenting feature and a further patient in whom confusion was not improved. In this patient, the abnormal mental

state was thought to be primarily due to dementia rather than lead poisoning. On seven occasions (five patients) no symptoms were present prior to chelation; six of these were second or third courses in individuals whose symptoms resolved during their first course of DMSA.

One course of DMSA was discontinued after 2 days due to the development of a mucocutaneous reaction. Soon after the second dose, the patient, who had no history of atopy or drug allergy, complained of pruritus affecting the neck. A semi-confluent erythematous rash developed over the neck and forearms in the ensuing hours, associated with a mild fever (37.9°C). There was no wheeze or other systemic effect and the white cell count was normal. Further DMSA was withheld. The following morning (~24 h after the second dose), the patient was apyrexial but had developed ulcers in the oropharynx. The opinion of an oral surgeon confirmed a probable adverse drug reaction that settled over 3–4 days with conservative treatment. The patient was not given further DMSA. This patient had received five previous courses (01–05) of DMSA, two of which (01, 02) had been discontinued before 5 days, since the patient found the sulphur smell of the tablets so unpleasant that she could not cooperate fully with treatment.

Baseline transaminase (ALT, AST) activity was increased (>50 IU/l) in 8 of 35 courses (range 56–189 IU/l). In six, the activity normalized during DMSA therapy, in one it remained stable and in the patient with a pre-treatment activity of 189 IU/l, there was a downward trend over 8 days to 121 IU/l at the end of the treatment.

Increased plasma transaminase activities were recorded during 5 of the 27 chelations (in four patients) for which baseline activity was normal. In four of these five, a value above the normal range was recorded on 1 day only (103 IU/l on Day 3, 53 IU/l on Day 4, 64 IU/l on Day 6 and 64 IU/l on Day 2), and subsequently normalized in three instances (not re-measured in the fourth). One chelation course was associated with a progressive increase in ALT activity from 41 IU/l baseline to 97 IU/l on Day 5 when chelation was discontinued (blood lead on Day 5 was 17 μg/dl). One week later, the ALT activity was 43 IU/l. All plasma creatinine concentrations measured before and during treatment were within the normal range.

In view of the occasional report of neutropenia in association with DMSA therapy,[28] a neutrophil count was checked before, during and after chelation, the latter within 2 days of completion of treatment in all but three cases when the interval between last DMSA dose and neutrophil count was 4–17 days. Neutropenia was not observed.

Although continuous 24-h urine collections were saved during all chelation courses, samples for six courses were discarded accidentally after measurement of the urine lead concentration. Patient compliance with urine collections was unreliable in a further two courses. Excretion data for zinc and copper during chelation were thus only available for 27 of 35 courses. Both mean daily urine zinc ($P = 0.013$) and copper ($P < 0.0001$) excretion were significantly increased by chelation. The 95% confidence intervals for the increases were 40.0–284.0 μg/24 h and 36.0–70.5 μg/24 h for zinc and copper, respectively. For individual courses, mean daily urine zinc excretion during chelation ranged from 0.7 to 5.3 (median 1.5, IQR 0.9–2.6) times the pre-chelation value, while the comparable values for copper were 0.9 and 9.6 times (median 3.1, IQR 2.3–4.3). This variation was observed not only between individuals but also in the same individual given repeated courses.

Serum zinc and copper concentrations for 35 courses of DMSA were measured before and during treatment. The serum copper concentrations were normal (0.7–1.6 mg/l) before treatment in all but one course (pre-chelation value 0.6 mg/l) in which it increased to within the normal range by the end of the treatment. In the remaining 34 courses for which data were available, in only one the serum copper concentration was marginally below the normal range (value 0.6 mg/l) by the end of the course. This patient received a further course of DMSA 2 weeks later during which the copper concentration returned to normal.

The pre-chelation serum zinc concentration was normal in 22 of 35 courses. In 17 of these serum zinc remained normal throughout chelation, while in three courses there was a transient fall to 0.6 mg/l during treatment (serum zinc was normal by the end of each of these courses). In two courses, no further serum zinc concentrations were measured after the pre-chelation sample.

For 13 of 35 courses, the pre-chelation serum zinc concentration was below the normal range of 0.7–1.6 mg/l with 9 values of 0.6 mg/l and 4 of 0.5 mg/l. In 11 of these, the daily serum zinc concentration fluctuated during chelation between 0.4 and 1.3 mg/l, though it was only below the normal range at the end of chelation in four cases (with values of 0.6 mg/l at the end of three courses and 0.5 mg/l at the end of one). In the 12th patient, who had a low pre-chelation zinc concentration, the values during treatment were normal. In the 13th case, no further serum zinc concentrations were measured.

Discussion

We report the largest case series of adult lead poisoned patients treated with DMSA 30 mg/kg/day in which comprehensive urine and blood data have been collected. The effect of chelation on urine lead excretion was the main outcome measure investigated, as this is the only easily measured parameter that can confirm a reduced body burden of lead. Furthermore, because it is known that there is a large variation in response to chelation,[22,23] it was considered mandatory to assess enhanced elimination with reference to individual pre-treatment values.

It has been customary, particularly in North America for a 19- to 26-day regimen to be employed in which DMSA 30 mg/kg/day is given for 5 days, then 20 mg/kg/day for 14–21 days[25–29] on the basis that treatment beyond 5 days at a lower DMSA dose will blunt the rebound in blood lead concentration that follows cessation of chelation. However, in 19 lead-poisoned children given DMSA 30 mg/kg/day for 5 days followed either by no further chelation ($n=7$), DMSA 10 mg/kg/day ($n=6$) for 14 days or DMSA 20 mg/kg/day ($n=6$) for 14 days, the mean blood lead concentration increased in all groups between Day 6 and 20.[30] Although this increase was less marked in the 20 mg/kg/day group than in the group receiving no treatment, 2 weeks later there was no significant difference in mean blood lead concentration between any group.

Farrar *et al.*[31] compared the effect on blood lead concentrations of the 19 day DMSA regimen ($n=7$ children) and two 5-day courses of DMSA ~30 mg/kg/day separated by 1 week ($n=4$). Four to six weeks after completion of therapy, blood lead concentrations had fallen significantly in both groups but the difference between treatments was not significant. This study is difficult to interpret because only two blood lead concentrations were measured per patient, the second at least 4 weeks after treatment.

As it has been demonstrated[21] that DMSA 30 mg/kg/day is significantly more effective than either 10 or 20 mg/kg/day both in terms of enhancing lead excretion and reducing blood lead concentrations, DMSA 30 mg/kg/day was administered to our patients. Graziano *et al.*[21] also showed that the typical rebound increase in blood lead concentration after DMSA therapy is largely complete within 1 week of the last dose. For this reason, a break of at least 1 week was interposed between each course to allow time for redistribution of lead from bone to soft tissues and blood.

The median increase in daily urine lead excretion was 12.0 times baseline (range 1.3–37.1). This is comparable with that observed by others. For example, Restek-Samarzija *et al.*[32] found a mean ± SD increase in urine lead excretion of 14.4 ± 4.3-fold (range 9.4- to 22.5-fold) in seven Croatian battery workers given oral DMSA 2100 mg/day (30 mg/kg/day if the body weight was 70 kg) for 5 days. Fournier *et al.*[22] recorded an increase in mean daily urine lead excretion of 4.5–16.9 times pre-chelation values in six patients given DMSA 30 mg/kg/day for 5 days. Restek-Samarzija *et al.*[32] found that the first dose of DMSA had the greatest impact on 24-h urine lead excretion in most (5/7) patients, as in the present series.

Some authors have observed a greater impact on urine lead elimination with DMSA therapy. In six occupationally poisoned men, Graziano *et al.*[21] found that the mean daily urine lead excretion was about 17 times (estimated from a graph) greater than the mean pre-chelation value after oral DMSA 30 mg/kg/day for 5 days. These men had similar pre-chelation blood lead concentrations (mean 79 μg/dl) to the patients in the present series (mean 75 μg/dl) suggesting that the greater effect was not due to higher pre-chelation blood lead concentrations. Moreover, five children with a mean blood lead concentration of 36 μg/dl showed an increase in mean urine lead excretion of approximately 16 times the mean pre-chelation value during oral DMSA 1050 mg/m^2/day (equivalent to 30 mg/kg/day) for 5 days.[24] Nineteen children (mean pre-treatment blood lead concentration 53 μg/dl) treated with the same regimen[30] had a mean daily urine lead excretion about 20 times greater than pre-chelation.

Chisolm,[33] described a series of 59 children with blood lead concentrations of 25–66 μg/dl who received a total of 116, 26–28 day courses of oral DMSA. DMSA was given in a dose of 1050 mg/m^2/day (~30 mg/kg/day) for the first 5 days, then 700 mg/m^2/day for 21–23 days. Urine lead excretion data (as the ratio of microgram lead: mg creatinine per sample) were available before and for a 6-h collection at the end of the first week of treatment in nine cases and showed a mean ± SD increase of 5.1 ± 2.9-fold (range 1.8- to 9.8-fold). The time of urine collections during chelation was not specified with respect to time after DMSA dosing and is therefore difficult to interpret. In addition, the children were being treated on an outpatient basis and compliance with therapy could not be assured.

Ten occupationally exposed workers (mean ± SD blood lead concentration 67.9 ± 8.8 μg/dl) showed a significantly ($P<0.0001$) increased mean ± SD urine lead excretion from 89.1 ± 62.3 μg/g creatinine to 885 ± 374 μg/g creatinine, measured 12 h after completion of a 5-day course of DMSA

(600 mg daily; 8.6 mg/kg/day assuming a body weight of 70 kg).[34] The mean ± SD increase was 14.2 ± 9.8 (range 6.3–33.5) times the pre-chelation value. Lead excretion was based on a spot urine sample rather than continuous collection.

Pre-treatment urine lead excretion might be expected to reflect readily-mobilizable lead and thus correlate with the amount of lead removed during chelation. This was found to be true in the present series (Spearman rank correlation coefficient of 0.82). In addition, pre-treatment blood lead concentrations correlated well (Spearman rank correlation coefficient 0.81) with 5-day urine lead excretion suggesting that the blood lead concentration is a good indicator of the DMSA-chelatable body lead burden. A similar positive correlation (Pearson's correlation coefficient $r = 0.73$) was present between the pre-treatment blood lead concentration and urine lead excretion in the seven patients investigated by Restek-Samarzija *et al.*[32]

In our patients, the blood lead concentration ($n = 32$) fell from a mean ± SD of 74.2 ± 19.9 μg/dl to 42.8 ± 23.7 μg/dl at the end of 5 days' treatment, a decline to 57.7% of the mean pre-chelation value. However, if individual post-chelation blood lead concentrations are utilized and expressed as the percentage of their respective pre-chelation concentration, the mean ± SD fall was to 55.4 ± 21.9% (range 9.4–102%).

This percentage fall is comparable with that reported by others. For example, the mean blood lead concentration in eight patients given DMSA 30 mg/kg day for 5 days fell to 51% of the mean pre-chelation value (from 93 to 48 μg/dl).[22] The mean blood lead concentration fell from 38 μg/dl pre-chelation to 17 μg/dl at the end of the first week, a decline to 45% of the pre-treatment value in 39 children administered 66 courses of DMSA with 'excellent and good compliance'.[33] At this point, the children had received 5 days' DMSA 30 mg/kg/day and 2 days' DMSA 20 mg/kg/day.

Several papers[35–37] have been published based on the data collected during a large trial involving multiple clinical sites across North America, in which 780 children aged between 12 and 33 months with blood lead concentrations between 20 and 44 μg/dl were randomized to receive either placebo ($n = 384$) or up to three 26-day courses of oral DMSA (30 mg/kg/day for 7 days then 20 mg/kg/day for 19 days, $n = 396$). Blood lead concentrations were measured on Days 7, 28 and 42 after the beginning of each course of DMSA. Thus, data on Day 7 were at completion of the 30 mg/kg/day part of the treatment. The blood lead concentration fell from a mean pre-treatment concentration of 26.5 ± 5 to ~13.5 μg/dl,[36] a fall to ~50% of the mean pre-chelation value which corresponds closely to the present results.

Graziano *et al.*[30] observed a greater decline in mean blood lead concentration to 39% of the pre-chelation mean (from 52.5 to 20.5 μg/dl) in 19 children administered DMSA 30 mg/kg/day for 5 days. Two smaller case series[21,32] also reported greater reductions in mean blood lead concentrations following 5 days of chelation with DMSA, to 27%[32] and 29%,[21] respectively, of the mean pre-chelation values. The greater effect in these studies is not easily explained. One[32] involved seven occupationally poisoned men with a mean ± SD pre-chelation blood lead concentration of 45.3 ± 8.9 μg/dl, which fell to 12.3 ± 2.5 μg/dl after 5 days DMSA 30 mg/kg/day. The other[21] involved six occupationally poisoned men in whom the mean ± SE blood lead concentration fell from 79 ± 5 μg/dl to 23.7 ± 7 μg/dl after 5 days of chelation with DMSA.

Su *et al.*[38] reported two children treated with the 19-day DMSA regimen in whom the follow-up blood lead concentrations were measured after the fifth dose of DMSA 30 mg/kg/day. The results can, therefore, be compared directly with data from the present series. In these children, the pre-treatment blood lead concentrations were 52 and 62 μg/dl, which fell to 18 and 21 μg/dl, respectively, after chelation, that is, the blood lead concentrations fell to 35 and 34% of the pre-treatment values.

In 10 occupationally exposed workers, the mean ± SD blood lead concentration had decreased from 67.9 ± 8.8 to 38.9 ± 7.2 μg/dl, that is, to 57.3% of the pre-treatment value, 12 h after the fifth daily dose of oral DMSA 600 mg (8.6 mg/kg/day assuming a body weight of 70 kg).[34]

Thirty-five Andean children living and working in a highly lead-contaminated environment had a mean ± SD blood lead concentration of 43.4 ± 18.3 μg/dl before a 10-day course of oral DMSA (about 8–15 mg/kg/day).[39] Three weeks after the last dose, the mean ± SD blood lead concentration was 34.3 ± 16.2 μg/dl, a decline to 79%. However, suboptimal treatment doses were employed, lead exposure continued during treatment and there was a delay of 3 weeks before measurement of the post-chelation concentrations. This delay would have allowed redistribution of lead from tissues to blood so that the mean blood lead concentration is likely to be higher than would have been the case if it had been measured immediately after treatment.

Studies which employed a 19-day course of DMSA (30 mg/kg/day for 5 days then 20 mg/kg/day for 14 days) provide data regarding the effect of prolonged chelation on blood lead concentrations. Six children given this regimen[30] had a mean blood

lead concentration at the end of treatment of ~50% of the mean pre-treatment value. Liebelt *et al.*[26] found that the mean blood lead concentration in seven children given 19 days of oral DMSA fell from 51 μg/dl (range 45–60) pre-chelation to 21 μg/dl after treatment, that is, to 42% of the pre-chelation value. In another study,[40] the mean blood lead concentration in 19 children fell from 34.9 ± 4.7 μg/dl pre-chelation to 27.4 ± 7.5 μg/dl ($n = 14$ for post-treatment concentration) 10 days after completion of the course, that is, to 78.5% of the pre-treatment value. The mean blood lead concentration 10 days after chelation was not significantly different from that found in children who received placebo.[40]

Headache, lethargy and constipation were the most frequently reported features associated with lead poisoning in the present series. Over half the patients described improvement or resolution of symptoms within the first 2 days of chelation and this is similar to that reported by others.[20,22,41] Since the first two DMSA doses in this study removed 40–60% of the total lead excreted over 5 days, symptomatic improvement within this time may be explained by removal of ready-chelatable lead. This may be the case for abdominal pain and constipation as circulating lead may influence gastrointestinal motility, but it is less easy to explain a rapid resolution of neurological features. However, experience with sodium calcium edetate in lead encephalopathy endorses the fact that significant and rapid reversal of cerebral toxicity occurs[11,15] even if the pharmacodynamics are not understood. The effect of chelation therapy on symptoms suggests that even though the percentage of the total body lead burden that is removed by chelation is small (which is particularly likely to be true in cases of chronic exposure when most lead is in bone), it is the compartment from which lead is being removed that is clinically important.

DMSA was generally well tolerated by our patients. The only major adverse effect was a mucocutaneous reaction that necessitated discontinuation of therapy after the two doses. The succimer data sheet (Lund beck Inc., Deerfield IL, USA) includes mucocutaneous eruption as one of several adverse reactions affecting 'skin and appendages' to have occurred in 325 patients (191 children and 134 adults). Twenty dermatological reactions were described involving 'papular rash,' herpetic rash', 'pruritus' or 'mucocutaneous eruptions' with thus an overall incidence of cutaneous reactions of 6%. One of these reactions was classified as 'mucocutaneous' and occurred after 'repeated' DMSA administration. Grandjean *et al.*[42] described a man with occupational lead poisoning who developed a mucocutaneous vesicular eruption on the second day of his third course of oral DMSA. Although the distribution of lesions was similar to Stevens Johnson syndrome, they did not have the classical 'target' outline nor was the patient as systemically unwell as usually seen with this condition. The mucosal lesions in our patient were confined to the mouth. Taking the present series together with the Grandjean report and the manufacturer's experience, three cases of a mucocutaneous reaction occurred among 343 patients, in each case after more than one course of DMSA. A further case of an urticarial rash after 14 days oral DMSA has been published.[43] These dermatological reactions to DMSA are probably best classified as fixed drug eruptions, the pathogenesis of which are poorly understood.[44]

In our patients, the most common adverse effect associated with DMSA was a transient rise in ALT activity (maximally to 103 IU/l) that occurred in five courses involving four different patients. In a further eight courses, involving seven patients, ALT activity was increased prior to commencement of chelation and either normalized or improved during treatment. No DMSA course had to be discontinued due to escalating liver enzyme activities. Others have reported mild increases in ALT activities in up to 57% of DMSA chelations[26] without clinically significant hepatic sequelae. The incidence appears to be higher in the paediatric population and probably in part reflects the wider range of values that occur in growing children. In keeping with this, Angle[45] reported pre-chelation rises in AST activity with fluctuations independent of therapy in 24 of 26 paediatric cases.

DMSA significantly increased both urine zinc (median increase 1.5 times pre-chelation) and copper (median increase 3.1 times pre-chelation) excretion. The increased elimination of zinc and copper showed wide individual variation (range 0.7–5.3 and 0.9–9.6 times pre-chelation for zinc and copper, respectively) but in no case was associated with symptoms. The serum zinc concentrations are difficult to interpret as they showed marked variability, an observation that is well recognized in those not being chelated.[46] In only 3 of the 22 cases, where the pre-treatment serum zinc concentration was normal, did the concentration fall below the normal range during chelation. Only in one of 34 cases where the pre-treatment serum copper concentration was normal did the serum copper concentration fall during treatment to below the normal range. In all cases, the serum concentrations returned to normal within a few days.

Few data are available from other studies. A significant increase ($P < 0.01$) in zinc excretion was

noted by Graziano *et al.*[21] in 12 men given either oral DMSA 20 or 30 mg/kg/day. The six men who received DMSA 20 mg/kg/day also showed a significant ($P < 0.05$) increase in urine copper excretion, though not surprisingly those who received 30 mg/kg/day. Individual values were not stated so the variation in effect was not known. No significant effect on copper and zinc elimination was found in 59 children given DMSA for 26–28 day courses (~30 mg/kg/day for 5 days then 20 mg/kg/day),[33] although assessment was by fractional rather than complete urine collections. Chisolm[33] reported 'no substantial increase in the output of copper and that the urinary output of zinc during (the first 5 days) therapy did increase perhaps 2-fold' in seven children given oral DMSA 30 mg/kg/day for 5 days then 20 mg/kg/day for 21–23 days.[36] Numerical data were not stated.

In 10 asymptomatic occupationally lead-poisoned men (mean pre-chelation blood lead concentration 67.9 μg/dl) administered oral DMSA 600 mg/day (~8.6 mg/kg assuming a body weight of 70 kg), the excretion of zinc and copper (measured as microgram per gram creatinine) 72 h after the first DMSA dose were increased significantly ($P < 0.0001$) compared with pre-treatment values. There was a greater effect on urine copper which showed a mean increase of 2.4-fold compared with baseline values while the mean increase in zinc excretion was 2.1-fold.[34] Serum concentrations of these metals were not measured.

Conclusions

Oral DMSA 30 mg/kg/day for at least 5 days increased urine lead excretion and reduced blood lead concentrations significantly, though there was wide inter- and intra-individual variation. DMSA was generally well tolerated, though chelation was associated with significant increases in urine zinc excretion and, to a greater extent, copper excretion but without a clinically important effect on serum concentrations of these trace elements. There was a transient increase in ALT activity during 5 of 35 (14%) chelations. A mucocutaneous skin reaction occurred on one occasion. The length of a DMSA 30 mg/kg/day course should ideally be tailored to an individual patient's response as indicated by assessment of urine lead excretion and blood lead concentration on Day 5, though 5 days chelation would appear to be a minimum. Lead-induced symptoms are unlikely to be present on Day five, though if they are, this would also support the continuing of DMSA. This approach requires regular clinical review and ready access to a laboratory able to undertake frequent analyses.

Oral DMSA 30 mg/kg/day is an effective antidote for lead poisoning though there is a wide inter-individual variation in response to chelation. To optimize the impact of treatment, and determine its length and identify adverse effects (notably those on zinc and copper excretion, on liver function and the skin), clinical and biochemical monitoring should be undertaken during chelation, though there is as yet no consensus internationally on the intensity of monitoring required.

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