Distribution of lead in body fluids after ingestion of soft solder

W I MANTON¹ AND C R MALLOY²

From the Department of Geology,¹ The University of Texas at Dallas, Richardson, Texas 75080, and the Department of Internal Medicine,² University of Texas Health Science Center at Dallas, Dallas, Texas 75235, USA

ABSTRACT Blood, serum, cerebrospinal fluid, and urine obtained from a patient before and after chelation therapy showed that (1) the ratio of Pb in his cerebrospinal fluid to that in his serum varied from 0.4 to 0.9 and was independent of serum Pb concentration; (2) the fraction of Pb in his serum fell linearly with decreasing blood Pb concentration and changed from 1.6% to 0.33% as his blood Pb concentration changed from 116 $\mu\text{g/dl}$ (5.6 $\mu\text{mol/l}$) to 31 $\mu\text{g/dl}$ (1.5 $\mu\text{mol/l}$); and (3) his renal clearance of Pb from serum varied from 5 ml/min to 36 ml/min. This high value was obtained 11 days after chelation and is attributed to large quantities of Sn in his urine promoting the excretion of Pb. Solder was identified in his stool after discovery of radio-opaque material in his bowel. The Pb isotope ratios of the solder were different from those in his urine when he was first admitted, and showed that he had ingested solder when he had returned home on weekend passes.

In the study of the human metabolism of Pb the precise, isotope ratio measuring mass spectrometer has been little used, but is none the less a valuable and versatile instrument. Recent work includes the study of Pb kinetics by oral administration of stable isotopes to healthy subjects,¹ the identification of the endogenous and exogenous components of Pb in blood through the natural variations in Pb isotope ratios,² and, by way of the technique of stable isotope dilution, the first accurate measurements of Pb in serum and cerebrospinal fluid.³ We report here an unusual case of Pb poisoning in which we used these mass spectrometric techniques.

Case history

The patient was a 60-year-old white man who complained of the abrupt onset of vertigo, slurred speech, and decreased sensation on the right side of his body. For the past two years his work as a plumber had included soldering and grinding soldered joints on copper pipe to a smooth finish. In January 1979 he left his job because of respiratory complaints attributed to bronchitis. When he developed neurological symptoms he was referred for

evaluation. He had smoked one packet of cigarettes a day for 40 years. His ethanol consumption was under 200 ml a week, and he always drank commercially distilled products. There was no history of hypertension, transient ischaemic attacks, headaches, nausea, or abdominal or seizure disorder. He was not taking any medicine.

Blood pressure was 166/90. He was a slender, alert, and co-operative man. Oral hygiene was poor, and the gingival margin was normal. There were no cutaneous signs of liver disease. Anteroposterior chest diameter was increased, and the cardiac examination showed nothing abnormal. The abdomen was soft without tenderness or masses, and the stool was guaiac negative. Neurological examination was remarkable for a mild right facial weakness (consistent with a central VII paresis), mild peripheral sensory neuropathy affecting his legs, and right-sided loss of temperature and pinprick sensation below the neck. There was no wrist or foot drop. The chest x-ray film was consistent with a chronic obstructive pulmonary disease, and initial abdominal films showed nothing abnormal. The serum K^+ was 4.7 meq/l and the creatinine 1.2 mg/100 ml. Serum aspartate transaminase (SGOT), lactate dehydrogenase, alkaline phosphatase, and bilirubin were normal. The haematocrit was 43.5% and there was no basophilic stippling of the red cells. Urine analysis showed nothing abnormal. Twenty-four-

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hour urine coproporphyrin was 1.17 mg/24 h (normal range 100-300 $\mu\text{g}/24\text{ h}$). Delta-aminolaevulinic acid screen was "moderately positive," but a repeat sample was negative. The initial computed tomogram (9 May 1979) showed a small arcuate region of low density in the left basal ganglia affecting the junction of the anterior and posterior limbs of the internal capsule. Electroencephalography showed nothing abnormal. Before a lumbar puncture performed as part of his routine evaluation the patient volunteered to be a control in a study of cerebrospinal fluid lead content in patients with amyotrophic lateral sclerosis. The study was approved by the appropriate committee of the University of Texas at Dallas. A repeat computed tomogram (3 July 1979) again showed the small low density region adjacent to the left internal capsule, which was thought to represent an area of lacunar infarction.

Initial cerebrospinal fluid, blood, serum, and urine Pb concentrations were raised. Six weeks later they had increased by 50% (table). The clinical impression was cerebrovascular disease and coexistent lead intoxication. Treatment with calcium disodium ethylenediaminetetraacetate (EDTA) (3000 mg intravenously over 10 hours) was started. Because the calcium salt of EDTA was not a formulary item, and therefore not available at all times, tetrasodium EDTA was substituted when needed. During the initial infusions serum Ca was monitored and did not change appreciably. During and after treatment Pb concentrations in urine, blood, serum, and cerebrospinal fluid were monitored. To determine the source of Pb intoxication, the isotope ratios of the Pb were measured. When it became apparent that the source was solder, an attempt was made to measure the patient's excretion of Sn. The results and their importance are discussed below.

The patient was treated daily for five days and sent

home for the weekends for a total of 15 treatments with EDTA. After the second week the patient returned from home and complained of vague abdominal discomfort. An abdominal x-ray examination on the seventeenth day of treatment showed fine metal-density particles scattered throughout the colon. A repeat x-ray examination (day 20) showed nearly complete disappearance of the particles. His stool collected during this period contained particles that were identified as solder.

In May 1980 neurological examination was remarkable only for diminished vibratory sense in the legs. Blood Pb was 31 $\mu\text{g}/\text{dl}$ (1.5 $\mu\text{mol}/\text{l}$). In October 1980 he suddenly developed aphasia and he fell once to the right. Aphasia resolved after two days, and examination at that time was remarkable for diminished vibratory sense in the arms and legs, mild ataxia, and poor performance of cerebellar testing in the legs. Blood Pb was 83 $\mu\text{g}/\text{dl}$ (4.0 $\mu\text{mol}/\text{l}$), and a repeat course of chelation therapy (with penicillamine) was administered.

Material and methods

LEAD ASSAYS

A 30 cm radius, 60° sector field mass spectrometer, and a clean chemical laboratory were used in this work. To measure Pb concentrations, we took 5 ml of blood, 10 ml of serum and cerebrospinal fluid, and 10-200 ml of urine, added a pure ^{206}Pb spike and decomposed by boiling with conc HNO_3 in Teflon FEP bottles. For blood and urine, the mixture of Pb isotopes was separated by $\text{Ba}(\text{NO}_3)_2$ coprecipitation and electrodeposition²; for serum and cerebrospinal fluid, separation was by ion exchange, using the same resin and columns as used for Sn (see below), except that the sample was loaded in and the column washed by 1.2N HCl. The Pb was stripped with 6N HCl. A

Summary of Pb and Sn concentrations in body fluids before and after chelation therapy

Date	Blood ($\mu\text{gPb}/\text{dl}$)	Serum ($\mu\text{gPb}/\text{dl}$)	CSF ($\mu\text{gPb}/\text{dl}$)	24-hour urine		Serum Pb Blood Pb %	CSF Pb Serum Pb	C_{Pbs} ml/min	Urine Sn Serum Pb
				μgPb	μgSn				
1979									
15 May	75.8	0.81	0.70	—	—	1.1	0.86	—	—
6 July	116	1.86	1.32	235	19	1.6	0.71	8.8	10
9-28 July	Patient treated with three courses of EDTA								
31 July	—	—	—	181	30	—	—	—	—
8 August	50.3	0.28	0.19	146	19	0.55	0.69	36	68
21 August	—	—	—	98	10	—	—	—	—
21 September 1980	50.8	0.24	—	—	—	0.47	—	—	—
22 February	47.2	0.29	—	22	3.7	0.61	—	5.1	13
18 May	30.9	0.10	—	25	6.0	0.33	—	17	60
30 September	82.5	1.93	0.76	215	16	2.3	0.39	7.7	8.3
6 October	70.3	1.11	—	111	23	1.6	—	6.9	21

C_{Pbs} = Clearance of Pb from serum.

large amount of organic material not decomposed by HNO_3 follows Pb through the column and has to be destroyed by HClO_4 . From the amount of crystalline residue this material clearly contains much complexed metal, but this does not interfere with the quality of the ionisation of Pb needed for acceptable stable isotope dilution runs. (Similar material greatly suppressed the ionisation of Sn, however, necessitating that all the organic material be destroyed before the ion exchange separation.) For the isotope ratio runs an aliquot of urine containing 1 μg of Pb was processed through the ion exchange columns and the Pb was further purified by electrodeposition. We report only the ratio of $^{206}\text{Pb}/^{207}\text{Pb}$ which, being close to unity, is the most accurately measured. The relative standard deviation averaged 0.06%. Blanks ranged from 1 to 2 ng Pb (5 to 10 pmol), negligible in the case of blood and urine, but not more than 10% of the Pb processed in serum and cerebrospinal fluid.

TIN ASSAYS

We found that Sn is ionised from an emitter of silica gel and phosphoric acid on an Re filament and that 1 μg Sn (8 nmol) gives an ion current of about 10 picoamps stable for 20 minutes. Ions of RbO are always present and interfere at mass 119. We therefore used a 97.8% enriched ^{118}Sn spike and measured the ratio $^{120}\text{Sn}/^{118}\text{Sn}$. Urine was first decomposed in 70% HNO_3 . An aliquot of 1%–2% of the daily output was spiked with 1 μg ^{118}Sn (8 nmol) and dried in a Teflon capsule. To prevent hydrolysis of Sn salts to intractably insoluble metastannic acid, the drying was carried out under a heat lamp. Five hundred microlitres of HClO_4 containing 0.25% H_2SO_4 were added to the residue, and the capsule was sealed with a tight-fitting lid containing an 0.4 mm diameter weep hole. The temperature was held at 180°C for 48 hours, by which time the oxidation of the organic residue was complete. If H_2SO_4 was not added more than 90% of the Sn was lost by volatilisation. ClO_4 ions, which have almost infinite binding coefficients with anion exchange resin, were removed as insoluble KClO_4 by adding 4 mmol of KCl for each per cent of the daily output in the aliquot. The sample was dried, dissolved in 2 ml of 6N HCl, centrifuged, and the supernatant was loaded on to an ion exchange column of Teflon, 6.3 mm diameter, containing Dowex 1×8 , 200–400 mesh to a height of 16 mm. After draining, the column was washed with three 0.5 ml portions of 6N HCl, followed by three 0.5 ml portions of 8N HF. Sn is retained on the column as the hexafluoride ion and is removed with 2 ml of 2N HNO_3 . The blank for this procedure is about 1 ng (8 pmol). Small amounts of Cd follow Sn. These are usually not a problem and burn off the filament while

Sn is ionising. When the patient was on chelation therapy, however, his urine contained so much Cd that sufficiently large amounts followed Sn so as to almost completely suppress its ionisation. We lost the majority of these runs, even though we put some samples through the ion exchange column twice.

Results

Before chelation, his urinary excretion of Sn and Pb averaged 20 and 230 $\mu\text{g}/24\text{ h}$, respectively. The $^{206}\text{Pb}/^{207}\text{Pb}$ ratio was constant at 1.171 (fig 1). On the first day of chelation (day 1) he excreted 12 mg Pb (0.58 mmol) and, with the exception of day 5, successively less on the succeeding five days. A small shift in isotope ratio was seen after day 1. His blood Pb initially increased to 123 $\mu\text{g}/\text{dl}$ (5.9 $\mu\text{mol}/\text{l}$) but fell to 45 $\mu\text{g}/\text{dl}$ (2.2 $\mu\text{mol}/\text{l}$) by day 5. On days 7 and 8, the weekend, the patient went home. The Pb content of his urine continued to decrease, but that of Sn increased. His isotope ratio attained the baseline value on day 7 but increased on day 8. Blood drawn the following morning, before resumption of chelation therapy, showed that the isotope ratio of the Pb in his body was rapidly changing. Except for a decline on day 10 the ratio in his urine increased to a maximum of 1.192 on day 12. It then declined until day 14, the first day of the following weekend when the patient again went home. On day 15, the Sunday, the isotope ratio of his urine increased and the following morning his blood Pb stood at 70 $\mu\text{g}/\text{dl}$ (3.4 $\mu\text{mol}/\text{l}$). On day 17, when solder was discovered in his bowel, the isotope ratio of Pb in his urine was again at a maximum value of 1.192. That of the solder was 1.197. During the three-day passage of the solder through his colon the isotope ratio and quantity of Pb in his urine declined. At the end of treatment his blood Pb had been halved and his serum and cerebrospinal fluid Pb reduced by a factor of nearly 7. Over the next six months his blood and serum Pb remained constant, while his urinary excretion of Pb and Sn declined appreciably. By May 1980 his blood Pb had fallen to 31 $\mu\text{g}/\text{dl}$ (1.5 $\mu\text{mol}/\text{l}$) but showed only a small change in isotope ratio (1.192) from the previous February (1.191) and August (1.187). At this time his urinary excretion of Pb and Sn was 25 and 6 $\mu\text{g}/24\text{ h}$, respectively (0.21 μmol and 0.05 μmol). Six unexposed subjects had excretions of Sn ranging from 1 to 6 $\mu\text{g}/24\text{ h}$ (8–48 nmol/24 h). When he returned with high blood Pb in September 1980 the isotope ratio was 1.240 and his urinary Sn was raised.

Metal recovered from his stool contained many curled, deeply striated shavings. All were somewhat corroded. Associated with the metal were grains of garnet. Shavings of Cu, conspicuous in the material

Fig 1 Upper portion: Ratio $^{206}\text{Pb}/^{207}\text{Pb}$ in blood and urine before, during, and immediately after chelation therapy. Isotope ratio of Pb in solder containing stool sample is also shown. Lower portion: Concentration of Pb in blood and urine and concentration of Sn in urine over same period. Note a different scale used to represent urinary Pb during chelation therapy and that after 28 July time scale is not continuous.

from his badge, were also present. Analysis of the bulk material gave 18% Sn and 82% Pb. During the first series' observations the fraction of Pb in the patient's serum changed from 0.3% of whole blood Pb to 1.6% as the whole blood concentration changed from 31 $\mu\text{g}/\text{dl}$ (1.5 $\mu\text{mol}/\text{l}$) to 116 $\mu\text{g}/\text{dl}$ (5.6 $\mu\text{mol}/\text{l}$). The second time his blood Pb was raised the fraction was larger and variable. A plot of Pb in serum

against Pb in blood is shown in fig 2. Blood taken 12 hours after administration of EDTA contained close to normal ratios of serum Pb to blood Pb. In one sample taken three hours after administration of EDTA had begun 6.4% of the Pb was contained in serum.

The concentration of Pb in cerebrospinal fluid varied between 39% and 86% of the serum concentration. Apart from the fact that the concentration of Pb in cerebrospinal fluid was consistently less than that in serum, no correlation appeared to exist.

The patient's renal clearance of Pb from serum ranged from 5.1 ml/min to 36 ml/min, the high value being obtained 11 days after the end of chelation therapy.

Discussion

SOURCE OF LEAD INTOXICATION

The change in isotope ratio during the third period of treatment is clearly attributable to the ingestion of Pb with a different isotope ratio from that stored in his tissues. The time of the change and the known two to three day transit of material through the alimentary tract⁴ suggest that the patient ingested the solder

Fig 2 Plot of serum Pb against whole blood Pb.

when home for the weekend. Noting that a rapid change in isotope ratio had occurred the previous weekend and that increases in isotope ratio accompanied increases in Pb excretion, we suspect that the patient ingested solder on that weekend also, and on days 5 and 12. Furthermore, the raised Sn in his baseline urines and in his urine of September 1980 suggested that the source of his lead intoxication on both occasions was also solder, even though he had not worked since January 1979. The isotope ratios, however, show that none of these three sources of solder was the same.

The baseline $^{206}\text{Pb}/^{207}\text{Pb}$ of 1.171 is unusually low for Pb in the Dallas environment, although it is at the lower end of the range, 1.167 to 1.310, that we have measured from soldered cans. Solder purported by the patient to have been used in his work had a ratio of 1.217 and filings caught between his identification badge and its plastic cover had a ratio of 1.194. Blood obtained from his workmate contained 16 μg Pb/dl (0.77 $\mu\text{mol/l}$) with a ratio of 1.196. Thus we cannot match the Pb in his blood with industrial exposure. Exposure at home seems unlikely as his wife's blood contained 12 μg Pb/dl (0.58 $\mu\text{mol/l}$) with a ratio of 1.199. Unfortunately, we did not measure the isotope ratio of the blood sample of 15 May, but, to obtain an estimate of how long his blood had so low a ratio, we obtained in August 1979 clippings of his toenails. These contained 9 ppm Pb with a ratio of 1.192. Given that nails grow at 0.1 mm/day,⁵ this ratio would have been that of his blood six to nine months earlier, or at about the time he was last working. We conclude that the patient acquired Pb with the ratio of 1.171 only a short time before he came to our notice in May 1979.

Taken together, the points discussed in the preceding paragraphs suggest to us that the patient had deliberately ingested solder before admission to hospital, during treatment, and a year after treatment. He has, however, consistently denied having done so.

ACTION OF EDTA ON THE SKELETON

Hammond *et al*⁶ and Hammond⁷ have shown that EDTA removes Pb from soft tissue in an indirect manner, chelating with a mobile pool of Pb in bone, which is then rapidly replenished by Pb from blood and other soft tissue. In terms of their model the isotope ratios of Pb in the 12-hour urine samples (fig 1), when administration of EDTA started, represent those of the skeletal pool. The substance EDTA is rapidly cleared from plasma, so that the 12-hour urine samples collected when administration of EDTA had ceased tend to have lower isotope ratios, because they contain some Pb with the baseline isotope ratio, which began to enter plasma from the erythrocytes

and the soft tissues. Samples taken more than 12 hours after administration of EDTA, such as blood on day 7 and urine on day 9, have the baseline isotope ratio and are samplings of soft tissue Pb in transit to the skeleton. Once the patient began ingesting solder, the EDTA bound with both skeletal Pb and the Pb entering the plasma from his gut; while EDTA was not being administered, Pb from solder continued to enter his plasma and together with soft tissue Pb replaced the Pb removed from his skeleton. The result was that by the end of the treatment the patient had replaced Pb of one isotope ratio in his skeletal pool with Pb of another isotope ratio, which thereafter dominated the isotope ratio of his blood. The blood sample of day 20 is conspicuous for having an isotope ratio greater than that of urine. Since this sample was taken 12 hours after administration of EDTA, this blood Pb is interpreted to be newly absorbed Pb from solder mixed with some soft tissue Pb.

One of the patient's premolars contained 56 ppm Pb with an isotope ratio of 1.207, which is probably representative of the Pb in his compact bone, as the half life of Pb in that region of his skeleton is of the order of tens of years. The constancy of the isotope ratio (1.171) of Pb in his urine during the first week of chelation indicates that EDTA did not chelate a significant fraction of the Pb bound in compact bone. This observation, taken with the decreasing amounts of Pb in his urine, suggests that the chelatable pool is of limited size and near constant in isotope ratio, the same conclusion as reached by Hammond.⁶ Interestingly the ratio in his tooth, which reflects the Pb to which he was exposed 40 to 50 years ago, is somewhat greater than that found in the blood of current Dallas residents.² From observations on seasonal changes in Pb isotope ratios in blood Manton² has inferred such a relationship.

SIGNIFICANCE OF LEAD IN SERUM AND CSF

Our result that the fraction of Pb in serum rises with blood Pb concentration does not support the findings either of Cavalleri *et al*⁸ who reported plasma Pb to be approximately constant at 3% of whole blood or of Rosen *et al*⁹ who reported plasma Pb to be independent of whole blood concentration. In the case of the patient reported here quadrupling of blood Pb brought about a sixteen-fold increase in serum Pb, which indicates that the toxicity of Pb, measured by the level of Pb in serum, rises as a very steep function of blood Pb concentration (fig 2). DeSilva¹⁰ has reported plasma Pb concentrations and plasma Pb to blood Pb fractions similar to those found in this laboratory.³ Her plot of plasma Pb concentration versus erythrocyte Pb concentration is similar in shape to ours. We suggest that her data

would have been better fitted by a power function passing through the origin than by the straight line with a negative intercept that she fitted.

It must be emphasised that our patient showed none of the classic signs of Pb intoxication. We interpret this to mean that he had only recently acquired a high blood Pb concentration and that the haematological and neurological effects of Pb take time to manifest themselves in adults.

In absolute terms the fraction of Pb in the patient's cerebrospinal fluid is somewhat higher than the figure of 0.46 ± 0.20 obtained in this laboratory from patients with normal blood Pb concentrations,³ with the implication that at high blood Pb the blood-brain barrier becomes less effective in keeping Pb out of cerebrospinal fluid. The variability observed probably reflects slow equilibration between Pb in plasma and Pb in cerebrospinal fluid. Although the concentration of Pb in the patient's cerebrospinal fluid was as high as 20 times normal, he displayed no central nervous system deficits that could unequivocally be attributed to Pb intoxication.

Measurement of Pb in serum and cerebrospinal fluid will only be useful clinically once a correlation with toxic effects has been established. In a case of plumbism from a retained bullet,^{11,12} where it can be certain that the patient maintained high blood Pb for a long time, the patient suffered severe motor neuropathy with a serum Pb of $3.3 \mu\text{g/dl}$ ($0.16 \mu\text{mol/l}$) or 25 times normal. At the same time his cerebrospinal fluid Pb was $2.6 \mu\text{g/dl}$ ($0.13 \mu\text{mol/l}$) or 64 times normal, yet he showed no severe central nervous system deficits. This single case suggests that serum Pb is a more critical parameter to monitor than cerebrospinal fluid Pb.

RENAL CLEARANCE OF LEAD

The range of renal clearance observed, $5.1\text{--}36.0 \text{ ml/min}$, is in accord with the findings of Vander *et al*¹³ that the greater part of Pb filtered by the kidney is reabsorbed. Nevertheless, the high value of 36 ml/min requires explanation.

Inspection of the data in the table shows this measurement to have been made 11 days after the end of chelation therapy at a time when the patient's urinary excretion of Pb was steadily decreasing while his serum Pb remained constant. Over the period of observation his creatinine clearance remained constant at 68 ml/min , ruling out change in glomerular filtration rate. The isotope ratio of Pb in the urine of 31 July (day 22) shows that the Pb excreted was not Pb with the baseline isotope ratio that had been sequestered in the renal tubular cells. The excretion of the divalent elements, Ca and Mg, whose metabolism might have been perturbed by Na_4EDTA were in the normal range and did not

correlate with Pb excretion.

The explanation seems to lie in an interaction of Pb and Sn. Our data show that the excretion of these elements was mutually dependent for the three weeks after chelation therapy (fig 1) and that the ratio of urinary Sn to serum Pb gives a fairly consistent pattern of following the Pb clearance (table). There are three possibilities regarding such an interaction: Sn may (1) promote the tubular secretion of Pb; (2) inhibit its tubular reabsorption; or (3) increase its ultrafilterability. Vander *et al*¹⁴ have shown that the uptake of Pb by renal slices *in vitro* is inhibited by Sn^{4+} . In such experiments, however, the uptake is through the basolateral and not the luminal membrane of the renal tubular cells, with the implication that the effect of Sn would be to inhibit the tubular secretion of Pb. We therefore feel that the first possibility is unlikely. To evaluate the second and third, the absolute concentrations of ultrafilterable Sn and Pb in plasma must be known. Our attempts to measure these have thus far been unsuccessful. We found Amicon ultrafiltration cones to contain large and variable amounts of Pb ($80\text{--}190 \text{ ng}$ or $0.4\text{--}0.9 \text{ nmol}$) and the amount of Sn in serum ($<1 \mu\text{g/dl}$ or $0.08 \mu\text{mol/l}$) is at the limit of measurement by conventional stable isotope dilution methods.

Conclusions

(1) In the United States where the Pb used in industry comes from many mines differing in geological age isotopic analysis may be used to identify Pb from different sources. This technique may be especially useful where litigation is concerned.

(2) The isotopic data support the model that EDTA acts upon a finite chelatable reservoir of Pb in the skeleton.

(3) Before serum Pb and cerebrospinal fluid Pb concentrations may be used clinically, correlation with toxic effects must be established. The assays, however, are difficult and are probably beyond the capability of all but a few clinical laboratories.

(4) Although the daily absorption of Sn from the diet is probably not large,¹⁵ the small quantity absorbed may none the less have the beneficial effect of increasing Pb excretion.

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