URINARY EXCRETION PATTERN OF TRIETHYLLEAD, DIETHYLLEAD AND INORGANIC LEAD IN THE TETRAETHYLLEAD POISONING

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Abstract: The fractional determination of triethyl lead, diethyl lead, inorganic lead and total lead in the urines of a patient with tetraethyl lead poisoning was performed by means of hydride generation-flameless atomic absorption spectrometry.

The chemical species of lead in the urine 21 days after the exposure comprised about 50% diethyl lead, about 48% inorganic lead and about 2% triethyl lead.

The fractional determination of triethyl lead, diethyl lead and inorganic lead in the urines of the patient after intravenous drip of 1000 mg of calcium ethylenediaminetetraacetic acid (Ca-EDTA) only once (30 days after the exposure) was also performed. Compared with the lead output 2 days before the treatment (28 days after the exposure), the total lead output in the urine during the 12 hours after the intravenous drip of Ca-EDTA was increased to about 4 times, with inorganic lead accounting for about 98% of the increased output but with no increase in triethyl lead or diethyl lead output.

Keywords: Tetraethyllead poisoning—Hydride generation—Urinary triethyllead—Urinary diethyllead—Ca-EDTA treatment

INTRODUCTION

Toxic psychosis is characteristic of tetraethyl lead poisoning. This poisoning differs from inorganic lead poisoning in that the typical manifestations of lead poisoning such as anemia, coproporphyrinuria and extensor paralysis are absent, and that sequelae are less frequent even in the severest patients if only they have survived. Furthermore, large amounts of lead are excreted into the stool and urine for a considerably long period from immediately after the exposure to the lead, compared to the excretion of lead in inorganic lead poisoning.¹⁾

It is also known that the clinical picture of this poisoning recovers mostly in parallel with the decrease in the lead output in the urine.¹⁾²⁾ Cremer (1959)³⁾ reported data suggesting that tetraethyl lead is chiefly metabolized in the liver into triethyl lead, which in turn acts on the central nervous system to cause the characteristic toxic psychosis. From their early experiments on rats, Bolanowska (1968)⁴⁾ showed that there are 2

metabolic pathways *in vivo* by which tetraethyl lead is degraded into triethyl lead and inorganic lead, and that this triethyl lead is liable to be accumulated *in vivo*. From the subsequent experiments on rabbits, Bolanowska and Garczyński (1968)⁵⁾ described that the amount of lead deposited in organs had already considerably decreased 4 days after the application of tetraethyl lead, and that the pattern of the lead deposition in man rather resembled that in rabbits than in rats.

Chiesura (1970)⁶⁾ assayed the urine of tetraethyl lead poisoning patients for lead by Bolanowska's method, and showed by an indirect means that diethyl lead accounted for about 70% of the lead output in the urine.

In a previous paper,⁷⁾ we demonstrated that the lead outputs in the urine and feces of rabbits given tetraethyl lead were markedly increased, compared with those in inorganic lead-treated rabbits, and that triethyl lead in no way contributed to this increased lead output; and from these findings, we came to think that the applied lead was most probably excreted as diethyl lead.

In the present study, the preserved urines of a patient with tetraethyl lead poisoning 21 days or more after the exposure to the lead were assayed for diethyl lead, triethyl lead, inorganic lead and total lead by hydride generation-flameless atomic absorption spectrometry as described in a previous paper.⁸⁾

MATERIALS

1. *Urine samples*

The urine samples were from the patient with tetraethyl lead poisoning who had been reported in our previous paper.⁹⁾ This patient was poisoned with tetraethyl lead on December 9, 1974, while engaging in the cleaning of an aviation fuel tank. He was then hospitalized for 2 months, and discharged with recovery. Table 1 shows the total lead outputs in the urine during the period between 20 and 196 days after the exposure to tetraethyl lead. In the present study, the preserved urines from the same patient 21 days and between 23 and 30 days after the exposure were assayed for triethyl lead, diethyl lead, inorganic lead and total lead. These urine samples had been preserved frozen in a freezer (at -20°C) for about 6 years. The urines 20 and 22 days after the exposure were not available in sufficient amounts for the determination. The urines 30 days after the exposure were those after the intravenous drip of 1,000 mg of Ca-EDTA only once.

2. *Preparation of standard alkyllead solutions*

Standard triethyl lead solution: Triethyl lead chloride (Alfa Divison, Ventron Corp., U.S.A.) was purified by recrystallization from water-alcohol. The purified triethyl lead chloride contained not more than 0.1% inorganic lead¹⁰⁾ and no diethyl lead ion¹¹⁾ (not more than 0.1%).

Standard diethyl lead solution: Diethyl lead dichloride was synthesized by Heap's

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Table 1. Urinary excretion of total lead in the tetraethyllead (TEL) poisoning.

Days after exposure to TEL	Chelating therapy	Urinary total lead		Urine volume ml	Urine specific gravity
		$\mu\text{g Pb/L}$	$\mu\text{g Pb/24 hours}$		
20th		586	—	—	1.031
21st		382	—	—	1.020
22nd		276	—	—	1.020
23rd		147	—	—	1.012
24th		199	786	3950	1.014
25th		144	432	3000	1.012
26th		98	382	3900	1.011
27th		149	536	3600	1.013
28th		169	507	3000	1.012
29th		161	467	2900	1.012
30th	Ca-EDTA	669	2060	3080	1.013
31st	Ca-EDTA	609	1720	2825	1.013
32nd	Ca-EDTA	494	1524	3085	1.012
33rd	Ca-EDTA	490	1268	2590	1.014
34th	Ca-EDTA	348	1198	3440	1.010
35th		201	512	2550	1.011
36th		177	549	3100	1.014
37th		158	387	2450	1.015
38th		150	405	2700	1.014
39th		120	360	3000	1.014
40th		69	209	3000	1.009
⋮		⋮	⋮	⋮	⋮
196th		37	81	2200	1.020

Ca-EDTA 1000 mg/day, i.v.

method¹²⁾ from tetraethyl lead (Strem Chemicals Inc., U.S.A.) via diethyl lead dibenzoate, and purified by recrystallization from water-alcohol. The purified diethyl lead dichloride contained not more than 0.3% inorganic lead and no triethyl lead ion (not more than 0.1%).

METHODS

The urines were assayed for triethyl lead, diethyl lead, inorganic lead and total lead by hydride generation-flameless atomic absorption spectrometry (Yamauchi *et al.*, 1981).⁸⁾

For the determination of diethyl lead and inorganic lead, the urines were pretreated so as to first acidify them and then extract only the lead components by extraction with organic solvents and then by back-extraction into the water layer.

The determination of triethyl lead and total lead required no pretreatment of the urines. However, the urines during the treatment with Ca-EDTA required pretreatment

for the determination of total lead.

RESULTS

Table 2 shows the concentrations of triethyl lead, diethyl lead, inorganic lead and total lead in the urines from the patient from 21 to 29 days after the exposure.

The ratios of these chemical species of lead to total lead in the urine 21 days after the exposure were: about 50% diethyl lead, about 48% inorganic lead and about 2% triethyl lead. Also in the urine 23 days after the exposure, diethyl lead accounted for about 51% of total lead (total lead=triethyl lead+diethyl lead+inorganic lead). Furthermore, in the urine 28 days after the exposure, inorganic lead accounted for about 85% ; diethyl lead, about 10%, and triethyl lead, about 5% of total lead.

Table 3 shows the 24-hour outputs of triethyl lead, diethyl lead, inorganic lead and

Table 2. Concentrations of triethyllead (Et3Pb⁺), diethyl lead (Et2Pb⁺⁺), inorganic lead (Pb⁺⁺) and total lead in urine in the TEL poisoning.

Days after exposure to TEL	Total Lead	Et3Pb ⁺	Et2Pb ⁺⁺	Pb ⁺⁺
	(μg Pb/L)			
21st	382	6	177	168
23rd	147	<1	71	68
24th	199	<1	71	138
25th	144	3	16	143
26th	98	10	8	98
27th	149	8	21	125
28th	169	8	14	125
29th	161	13	<5	143

Table 3. 24 hours excretion of Et3Pb⁺, Et2Pb⁺⁺, Pb⁺⁺ and total lead in urine in the TEL poisoning.

Days after exposure to TEL	Total Lead	Et3Pb ⁺	Et2Pb ⁺⁺	Pb ⁺⁺
	(μg Pb/24 hours)			
21st	—	—	—	—
23rd	—	—	—	—
24th	786	<4	280	545
25th	432	9	48	429
26th	382	39	31	382
27th	536	29	76	450
28th	507	24	42	375
29th	467	38	<15	415

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total lead in the urines of the same patient between 21 and 29 days after the exposure. The 24-hour outputs of these chemical species between 21 and 23 days after the exposure were not available because the urine amounts during this period were indefinite.

Table 4 shows the concentrations of triethyl lead, diethyl lead, inorganic lead and total lead in the urines from the same patient following the intravenous drip of 1,000 mg of Ca-EDTA only once 30 days after the exposure. On this day, the urine was collected at each spontaneous voiding after the intravenous drip of Ca-EDTA at noon, and assayed for triethyl lead, diethyl lead, inorganic lead and total lead.

In the urine at 13:20, inorganic lead accounted for about 98%; triethyl lead, about 0.6%, and diethyl lead, about 0.6% of total lead. In the urine at 22:30, inorganic lead made up about 97%, and triethyl lead, about 3% of total lead. No diethyl lead was detected (N.D. < 5 $\mu\text{g Pb/liter}$).

Table 5 shows the outputs of triethyl lead, diethyl lead, inorganic lead and total lead in each urine after the intravenous drip of Ca-EDTA on the same day.

In the urines between 13:20 and 22:30, the output of inorganic lead was increased to about 5 times the output on the preceding day. The output of triethyl lead, however,

Table 4. Concentrations of Et₃Pb⁺, Et₂Pb⁺⁺, Pb⁺⁺ and total lead in urine after intravenous drip of Ca-EDTA (30 days after exposure to TEL) in the TEL poisoning.

Days after exposure to TEL	Time of collection	Total Lead	Et ₃ Pb ⁺	Et ₂ Pb ⁺⁺	Pb ⁺⁺
		(μg Pb/L)			
30th	13:20	1368	8	9	1429
	15:05	3737	12	35	3571
	16:00	397	11	8	393
	18:00	421	11	14	413
	22:30	316	11	<5	325
	03:20	—	—	—	—

Table 5. Urinary excretion amounts of Et₃Pb⁺, Et₂Pb⁺⁺, Pb⁺⁺ and total lead during each collection time after intravenous drip of Ca-EDTA in the TEL poisoning.

Days after exposure to TEL	Time of collection	Total Lead	Et ₃ Pb ⁺	Et ₂ Pb ⁺⁺	Pb ⁺⁺
		(μg Pb)			
30th	13:20	643	4	4	671
	15:05	561	2	5	536
	16:00	199	6	4	197
	18:00	202	5	7	198
	22:30	269	9	<4	276
	03:20	—	—	—	—

remained almost the same as that on the preceding day. The output of diethyl lead remained almost the same as that 2 days before (28 days after the exposure).

In the urines 21 and 23 days after the exposure to tetraethyl lead, diethyl lead accounted for about 50% of total lead, respectively. In the urine 28 days after the exposure, however, diethyl lead was decreased to about 10% of total lead.

The intravenous drip of Ca-EDTA resulted in an increased output of inorganic lead in the urine but no increase in either triethyl lead or diethyl lead.

DISCUSSION

The urine samples used in the present study were those that had been preserved in a freezer (at -20°C) for about 6 years since the days of collection until the day of assay. The assays attained in the present study show the output patterns of triethyl lead, diethyl lead and inorganic lead in the urines of a patient with tetraethyl lead poisoning.

Because triethyl lead, diethyl lead, inorganic lead and total lead were assayed for by different specific methods, the sum of the assays of triethyl lead, diethyl lead and inorganic lead did not always agree to the total lead value.

It has been shown by an indirect method that tetraethyl lead is metabolized *in vivo* into diethyl lead via triethyl lead; but there is no report of the direct determination of this diethyl lead as a metabolite. Chiesura⁶⁾ described that precipitable lead (inorganic lead) accounted for 20%; benzene-extractable lead (triethyl lead), about 10%, and unprecipitable lead (organic lead), about 80 to 90% of total lead in the urine of patients with tetraethyl lead poisoning, and that the difference between the amount of this unprecipitable lead and that of the benzene-extractable lead represented the amount of diethyl lead.

In the present study using hydride generation-flameless atomic absorption spectrometry, diethyl lead made up about 50% of total lead in the urine of a patient with acute lead poisoning 21 days after exposure to tetraethyl lead. The ratio of this content was slightly low, compared with the amount of diethyl lead (about 70 to 80%) as estimated by Chiesura. In the subsequent urines, the ratio of diethyl lead to total lead decreased gradually.

On the other hand, in another experiment to be published elsewhere, the analysis for the chemical species of the lead excreted in the urine of rabbits after administration of tetraethyl lead revealed that diethyl lead accounted for about 69%, inorganic lead for about 27%, and triethyl lead for about 4% of total lead 1 day after the administration, and the ratios of these lead components to total lead remained mostly unchanged during the first 7 days after the administration.¹³⁾

The urines after intravenous drip of Ca-EDTA (30 days after the exposure) were then assayed for different chemical species of lead. The total lead output in the urines on this day were increased to about 4 times the output on the 2 days before (28 days after the exposure). In this instance, inorganic lead made up the most part (98%) of

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total lead. On the other hand, neither triethyl lead nor diethyl lead was found increased.

EDTA produces metal chelate compounds with inorganic lead ions. However, no chelating reaction is said to occur between EDTA and triethyl lead or diethyl lead.³⁾ Triethyl lead and diethyl lead, with their ethyl groups bound to the lead atom acting as interfering factors, seem likely to form imperfect chelates with EDTA.

Therefore, the administration Ca-EDTA for the treatment of tetraethyl lead poisoning may accelerate the elimination of inorganic lead out of the body but not of triethyl lead and diethyl lead.

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REFERENCES

- 1) Machle, W.F. (1935). *J. Am. Med. Assoc.*, **105**, 578.
- 2) Sanders, L.W. (1964). *Arch. Environ. Health*, **8**, 270.
- 3) Cremer, J.E. (1959). *Br. J. Ind. Med.*, **16**, 191.
- 4) Bolanowska, W. (1968). *Br. J. Ind. Med.*, **25**, 203.
- 5) Bolanowska, W. and Garczyński, H. (1968). *Medycyna Pracy*, **19**, 235. (In Polish)
- 6) Chiesura, P. (1970). *Medicina del Lavoro*, **61**, 437. (In Italian)
- 7) Yamamura, Y., Arai, F., Yoshida, M. and Shimada, E. (1979). *St. Marianna. Med. J.*, **7**, 12. (In Japanese)
- 8) Yamauchi, H., Arai, F. and Yamamura, Y. (1981). *Ind. Health*, **19**, 115.
- 9) Yamamura, Y., Takakura, J., Hirayama, F., Yamauchi, H. and Yoshida, M. (1975). *Jpn. J. Ind. Health*, **17**, 223. (In Japanese)
- 10) Imura, S. and Fukutaka, K. (1965). *Bunseki Kagaku*, **14**, 1167. (In Japanese)
- 11) Imura, S., Fukutaka, K. and Kawaguchi, T. (1969). *Bunseki Kagaku*, **18**, 1008. (In Japanese)
- 12) Heap, R., Saunders, B.C. and Stacey, G.J. (1951). *J. Chem. Soc.*, 658.
- 13) Arai, F., Yamamura, Y. and Yoshida, M. (1981). *Jpn. J. Ind. Health*, to be published. (In Japanese)