

BRIEF REPORT

Urinary trimethyl tin reflects blood trimethyl tin in workers recycling organotins

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Abstract

Aim: Our recent case report of organotin intoxication showed higher ratio of urinary trimethyl tin (TMT) to dimethyl tin (DMT) than those of the previous cases exposed to only DMT, suggesting co-exposure to DMT and TMT occurred. The present study investigated how urinary TMT and DMT reflect blood TMT and DMT, respectively, to evaluate them as biomarkers for TMT/DMT exposure.

Methods: DMT and TMT from blood collected at different time points from three patients intoxicated with organotins were measured with HPLC-ICP/MS. Previously published data of urinary DMT and TMT were used for comparison. Regression analyses were conducted with dependent variable of blood DMT and TMT and independent variable of urinary DMT and TMT, respectively. Multiple regression analysis with dummy variables of individual was also conducted.

Results: Regression analysis did not show significant relation of urinary TMT to blood TMT or relation of urinary DMT to blood DMT, although the former was marginal. Multiple regression analysis showed significantly positive relation of urinary TMT to blood TMT.

Conclusions: The study shows that urinary TMT reflects blood TMT. In co-exposure to TMT and DMT, urinary TMT can be an internal exposure marker of TMT, which might be not only derived from external exposure to TMT but also converted from DMT in human body.

KEYWORDS

dimethyl tin, encephalopathy neurotoxicity, organotin, trimethyl tin

1 | INTRODUCTION

Along with recently introduced regulation to lead as a stabilizer to polyvinyl chloride, dimethyl tin (DMT) came to be used as an alternative to lead. Numerous cases of encephalopathy due to trimethyl tin (TMT) and DMT have been reported¹⁻³ and our previous studies demonstrated

encephalopathy of workers exposed to DMT⁴ and transformation of DMT to TMT in experimental animals.⁵ Recently, we reported encephalopathy in workers in organotin recycling factory,⁶ and assumed that they were exposed to mixture of DMT and TMT based on higher ratios of urinary TMT/DMT than those of previous cases exposed to only DMT.⁴ We consider it meaningful to add a report here on blood TMT or

DMT level of the cases, as it remains elusive how urinary TMT or DMT reflects blood TMT or DMT.

The present study investigated the relationship between blood and urinary organotins to evaluate how urinary DMT or TMT reflects blood DMT or TMT.

2 | SUBJECTS AND METHODS

2.1 | Profiles of three patients

Disease histories and present illness of the patients are described in detail in our previous study⁶ and the profiles of three patients are presented in Table S1. Briefly, all of them worked in the process of smelting organotins to produce inorganic metal tin ingots and were exposed to organotin fumes, although labor intensities and job description were different among them. The workers were exposed to fumes of organotin scraps for several weeks prior to the onset of symptoms. Their exposure to organotin was terminated at the end of October. Patient A was sent to emergency room with amnesia after experiencing myalgia and dizziness. His short-term memory was deficient, while long-term memory was intact. Dysfunction of verbal memory persisted at 4 weeks after symptom onset. Patient B experienced headache and dizziness followed by reversible amnesia for 3 or 4 days. Patient C complained of headache and dizziness but did not of amnesia and his symptoms were milder than Patient A or B. Urine and blood were collected from the patients after admission to the hospital. The data of urine were reported previously.⁶ This report was exempted from review by the Institutional Review Board of Ulsan University Hospital and Tokyo University of Science, because the blood was obtained only for diagnostic purpose but not for research.

2.2 | Chemicals

Inorganic tin (In-Sn), trimethyl tin chloride (TMTC), triethyl tin chloride (TETC), HNO₃ (60.0%–62.0%), pyridinedicarboxylic acid, and ultrapure water (for ultra-trace analysis) were purchased from Wako Pure Chemical Industries (Osaka, Japan). NH₄NO₃ was purchased from Kanto Chemical Co. Inc (Tokyo, Japan), monomethyl tin trichloride (MMTC) was purchased from Sigma-Aldrich (St. Louis, MO), and dimethyl tin chloride (DMTC) was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan).

2.3 | Preparation of blood samples

Blood was centrifuged at 15 000 G for 10 minutes and the obtained supernatant was diluted with ultrapure water three times. The resultant samples from blood were passed through a filter (0.45 µm, GL Science, Tokyo, Japan), and placed into polypropylene (PP) vial for analysis.

2.4 | Speciation analysis of organotins

Speciation analysis of blood methyltin and TET was performed using a combination of high performance liquid chromatography (HPLC, model HP1100, Hewlett Packard, Palo Alto, CA) and inductively coupled plasma mass spectrometry (ICP-MS, NexION 300S, Perkin Elmer, Waltham, MA) following previous studies.^{4–6}

2.5 | Calculation of half-life in one compartment model

The half-lives of blood DMT and TMT were calculated as $t_{1/2} = \ln 2 / K_e$, which is derived from the formula: $C_p(t) = A \times e^{(-K_e \times t)}$ ($C_p(t)$ = concentration in plasma at defined time interval after the time of known concentration corresponding to A; A = anchor concentration, which is known or estimated concentration at anchor point; e = base of natural logarithms; K_e = elimination rate constant; t = selected time after time of anchor concentration).

2.6 | Comparison with urinary DMT and TMT

Previously published data of urinary TMT and DMT⁶ were used for comparison of blood and urinary organotins in the ratios or regression analyses.

2.7 | Statistical analysis

Single regression and multiple regression were conducted using JMP version 11.0 (SAS Institute Inc, Cary, NC). Dummy variables were used for defining the individual factor, as Patient [A-C] is 1 for patient A, –1 for patient C or 0 otherwise, and Patient [B-C] is 1 for patient B, –1 for patient C or 0 otherwise.

3 | RESULTS

DMT and TMT were detected in blood of all workers, but neither of inorganic tin, monomethyl tin or triethyl tin was detected in any examined samples of blood. Blood concentrations of DMT and TMT are shown in Table S2. DMT and TMT decreased time-dependently in patient A and B, and patient C showed lower blood DMT and TMT than the other cases, which corresponded with milder degree of clinical symptoms in patient C than those of other patients. Calculation together with the previous data of urinary TMT and DMT⁶ shows the ratios of urinary TMT to blood TMT ranged from 2.0 (patient A on November 21) to 5.5 (patient C), which were smaller than the ratios of urinary DMT to

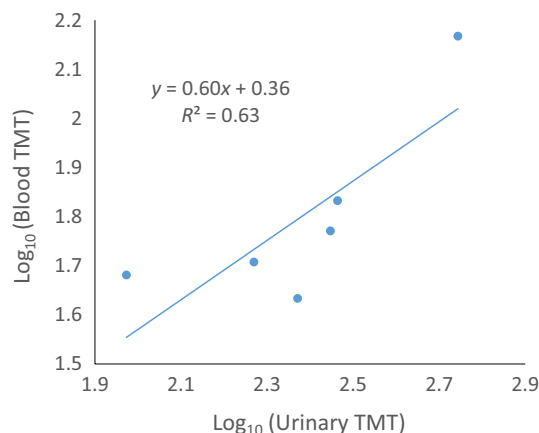


FIGURE 1 Relations of blood trimethyl tin (TMT) and urinary TMT. Simple regression analysis was conducted with independent variable of urinary TMT and dependent variable of blood TMT after logarithmic transformation. Least square method was applied to the difference of real value and estimated value of $\text{Log}_{10}[\text{Urinary TMT}]$. Equation of regression line: $\text{Log}_{10}[\text{Blood TMT}] = 0.60\text{Log}_{10}[\text{Urinary TMT}] + 0.36$ $R^2 = 0.63$, P value for test on slope of regression line = 0.06

blood DMT ranging from 12 (patient B on November 12) to 60 (patient A on November 13). The ratios of urinary TMT to DMT ranged from 1.6 to 6.3, while the ratios of blood TMT to DMT ranged from 5.9 to 59. Half-lives of blood TMT and DMT are shown in Table S3. In patient A, half-life of blood TMT was shorter than that of blood DMT, but the opposite tendency was observed in patient B.

Simple regression analyses after logarithmic transformation did not show significant relation of urinary TMT and blood TMT ($P = 0.06$, Figure 1), urinary DMT and blood DMT ($P = 0.09$, Figure S1), urinary TMT and blood DMT ($P = 0.80$), or urinary DMT and blood TMT ($P = 0.13$).

To remove possible effects of individual factor, multiple regression analyses were conducted with a model of the dependent variables of blood TMT or DMT and independent variable of urinary TMT or DMT and independent dummy variables of individual factors (Table 1). The results show significant effect of urinary TMT on blood TMT, but the

similar effect was not significant in the relation between urinary DMT and blood DMT, as well as between urinary TMT and blood DMT and urinary DMT and blood TMT (data not shown).

4 | DISCUSSION

The result shows urinary TMT reflects blood TMT better than urinary DMT reflects blood DMT. Given the fact that TMT is more neurotoxic than DMT, the present study suggests urinary TMT is not only a good biomarker of internal exposure to TMT but also a marker predicting the adverse effects of TMT or DMT exposure. Moreover, effectiveness of TMT as biomarker is strengthened by our previous studies showing conversion of DMT into TMT in experimental animals⁵ and probably also in humans.⁴

In the previous study, cases exposed to only DMT showed urinary TMT ranging from 74.6 to 946.3 $\mu\text{g/gCr}$ and urinary DMT ranging 39.0 to 779.4 $\mu\text{g/gCr}$.⁴ The ratios of urinary TMT to urinary DMT in cases ranging from⁴ 0.43 to 2.3 are much lower those in the present cases,⁶ suggesting that not only exposure to DMT but also co-exposure to TMT may have occurred. This is also supported by the comparison of blood DMT and TMT levels between the present study and the previous study. Cases exposed to only DMT showed blood TMT ranging from 10.9 to 327.5 and blood DMT ranging from 5.4 to 39.6.⁴ The ratio of blood TMT to blood DMT in them ranged from 2.0 to 8.3, which was smaller than those ranging from 5.9 to 59 in the present study.

However, the present study has several limitations. First, the number of workers was small, although multiple regression analyses confirmed the significant relation of urinary TMT and blood TMT. Second, we were not able to measure exposure concentration, although exposure of the workers to organotin was expected based on identification of organotin scraps that the workers smelted.

In conclusion, urinary TMT reflects blood TMT in humans exposed to organotin, suggesting urinary TMT might be a good biomarker for exposure to DMT and TMT and prediction of DMT/TMT-induced neurotoxicity.

TABLE 1 Parameter estimates in multiple regression analyses

Dependent variable	independent variable							
	Urinary TMT		Urinary DMT		Patient [A-C]		Patient [B-C]	
	Parameter estimate	P value	Parameter estimate	P value	Parameter estimate	P value	Parameter estimate	P value
Blood TMT	0.21	0.038	—	—	14	0.22	−1.0	0.92
Blood DMT	—	—	0.072	0.21	−2.4	0.28	1.8	0.40

Patient [A-C] is 1 for patient A, −1 for patient C, 0 otherwise, Patient [B-C] is 1 for patient B, −1 for patient C, 0 otherwise.

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DISCLOSURE

Approval of the research protocol: This report was exempted from review by the Institutional Review Board of Ulsan University Hospital and Tokyo University of Science, because the blood was obtained only for diagnostic purpose but not for research. *Informed consent:* N/A. *Registry and the registration no. of the study/trial:* N/A. *Animal studies:* N/A. *Conflict of interest:* There are no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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