

BRIEF REPORT

Indium concentration in serum is an excellent predictor for assessing accumulated indium concentration in the lungs

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Abstract

Objective: To clarify whether indium in serum (In-S) is an appropriate parameter for assessing accumulated indium concentration in the lungs (In-L).

Methods: During our approximately 15-year Japanese cohort follow-up, five male indium-tin oxide (ITO) or/and indium trioxide-exposed workers underwent lung surgical procedures to treat lung diseases or to confirm a diagnosis of lung impairments. We measured In-L of these Cases 1-5 and were able to assess the relationship between In-L and the most recent In-S. Another 1 Japanese case (Case 6) exposed to indium trioxide and indium hydroxide was referred from an article.

Results: Cases 1 and 3 had lung cancer, Case 2 suffered from recurrent pneumothorax, and Case 4 had interstitial pneumonia with mild emphysema. Case 5 had severe emphysema with pulmonary hypertension and underwent bilateral lung transplantation. In Cases 1-5, In-L and In-S ranged from 3.4 to 161.2 µg/g wet weight and 0.7 to 60.4 ng/mL, respectively, and In-L/In-S ratios ranged from 2484 to 4857. The slope of the single regression equation with zero intercept was 2767 and the correlation coefficient was 0.995. In contrast, Case 6 was extraordinarily outlying, but the reason is unclear.

Conclusions: In-S is an excellent predictor for assessing indium load in the lungs in ITO or/and indium trioxide-exposed workers. However, number of cases was only five and not enough to authorize definite conclusion. It is desirable to add more cases to confirm our conclusion.

KEYWORDS

correlation study, indium in serum, indium in the lungs

1 | INTRODUCTION

In 2001, a worker exposed to hardly soluble fine dusts of indium-tin oxide (ITO) died of bilateral pneumothorax

secondary to interstitial pneumonia.¹ In the wake of this case, efforts to pinpoint a causal relationship between exposure to hardly soluble indium dusts and lung diseases have been undertaken. Our epidemiological base-line studies clearly

Abbreviations: In-L, Indium concentration in the lungs; In-S, Indium concentration in serum; IP, Interstitial pneumonia; ITO, Indium-tin oxide; LC, Lung cancer; PE, Pulmonary emphysema; VATS, Video-assisted thoracic surgery.

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demonstrate the causal relationships,²⁻⁴ and indium in serum (In-S) was chosen as a biological exposure parameter.⁵

Our cohort study newly revealed progression of pulmonary emphysema in highly indium-exposed workers^{6,7} but failed to identify the effects of indium on other organs. Because we cannot actually measure indium concentrations in workers' lungs (In-L), which is only one target site, it is of great concern whether In-S is an appropriate parameter for assessing In-L. However, during our approximately 15-year cohort follow-up, 5 male ITO or/and indium trioxide-exposed workers in our cohort underwent lung surgical procedure and we were able to assess the relationship between In-S and In-L in these cases.

2 | METHODS

The cohort study was approved by the Kyushu University Certified Institutional Review Board for Clinical Trials (approval number 30-69), and by the Ethics Committee of the School of Medicine, Keio University (approval number 20110268). Written informed consent for using epidemiological and clinical data were obtained from all five cases after showing his own data to each case.

We conducted a baseline survey in 11 factories that handled indium from 2003 to 2006 with follow-up until 2018. During the follow-up periods, five ITO or/and indium trioxide-exposed workers underwent lung surgical procedures to treat lung diseases or to confirm a diagnosis of lung impairments.

An exenterated lung tissue sample was digested with 4 mL of 68% ultra-pure nitric acid (TAMAPURE-AA-100, Tama Chemicals Co) and 2 mL of 35% ultra-pure hydrogen peroxide (TAMAPURE-AA-100) using a microwave digestion apparatus. The digested samples were diluted to 20 mL with ultra-pure water, and then further diluted by 13% ultra-pure nitric acid with added rhodium solution as an internal standard. The final concentration of rhodium was set at 0.5 ng/mL. All samples (Cases 1-6) were analyzed by inductively coupled plasma mass spectrometer (ICP-MS; Agilent 7500c, Agilent Technologies Japan, Ltd.) at the Center of Advanced Instrumental Analysis at Kyushu University. To measure In-S, 0.5 mL of serum was digested and analyzed as the same way described above for the lung tissue pretreatment.

3 | RESULTS

Table 1 shows the profiles, clinical/pathological conditions, surgical intervention, In-L, In-S, and In-L/In-S ratio for each case. Cases 1-5 were participants in our cohort study and Case 6 was referred from an article.⁸ All cases were male and had been exposed to hardly soluble indium compounds

such as ITO, indium trioxide and/or indium hydroxide. Cases 1 and 3 had lung cancer and Case 2 suffered from recurrent pneumothorax. Case 4 had interstitial pneumonia (IP) and mild pulmonary emphysema (PE). Case 5 had severe PE with pulmonary hypertension and underwent bilateral lung transplantation.^{9,10}

Pulmonary segments of the exenterated samples were informed by surgical operators. The time lag between lung sampling and blood sampling was 0 days to 2 months. The number of measured lung sample portions was 1 to 6 depending on the case, and arithmetic means were used for analysis. In Cases 1-5, the ranges of the arithmetic mean for In-L and In-S were 3.4 to 161.2 $\mu\text{g/g}$ wet weight and 0.7 to 60.4 ng/mL, respectively, and In-L/In-S ratios ranged from 2484 to 4857. Figure 1 is a scatter chart of In-S (ng/mL) and In-L (ng/g wet weight). The slope of the single regression equation with zero intercept in Cases 1-5 was 2767 and the correlation coefficient was 0.995. In contrast, In-L/In-S ratio in Case 6 was 247, less than one-tenth of the ratios observed in Cases 1-5.

4 | DISCUSSION

Since the weight of 1 mL serum is approximately 1 g, In-L per unit weight (ng/g wet weight) was approximately 3000 times higher than In-S (ng/mL) in our five cohort participant cases. In-S was highly correlated with In-L, confirming that In-S is an excellent biological parameter for presuming the indium load in the lungs. The longest time lag between lung tissue sampling and blood sampling was 2 months (Case 4). This time lag is considered to be negligible because the biological half-life of In-S (>10.0 ng/mL) in workers who have left indium exposure jobs has been found to be approximately 9 years.⁷

In Case 6, In-S was high but the In-L/In-S ratio was significantly low and the data for Case 6 in Figure 1 were extraordinarily outlying compared to those of other five cases. We have no clear explanation for this discrepancy. As shown in Table 1, the distribution of In-L is wide depending on the sampled segments. For example, In-L ranged from 38.4 to 169.2 $\mu\text{g/g}$ in Case 4 and from 53.8 to 211.2 $\mu\text{g/g}$ in Case 5. Thus, it is possible that the particular portion sampled in Case 6 was a fortuitously low indium region and unsuitable for assessing In-L. There may also have been an effect related to the difference in bioavailability and kinetics between ITO/indium trioxide and the indium hydroxide to which Case 6 was exposed, though to best of our knowledge, no supporting information is available in either human or animal studies.

We believe that In-S is an excellent predictor for assessing indium load in the lungs in ITO or/and indium trioxide-exposed workers. However, the present study included only five cases, which is not enough to authorize a definite conclusion. More cases must be studied in order to confirm our conclusion.

TABLE 1 Case profiles and indium concentrations in exenterated lung tissues and in serum

Case	Age	Smoking	Indium exposure	Indium exposure duration	Clinical diagnosis	Surgical treatment		Location of sampling sites and indium in the exenterated lung tissue ($\mu\text{g/g}$ wet weight)	In-L ($\mu\text{g/g}$ wet weight)	In-S (ng/mL)	In-L/In-S ratio	Lag	Source
						Site	Procedure						
1	60	Never	ITO	3 mo	LC	Right upper lobe	VATS	Apical: 2.6, Anterior: 3.4, Posterior: 4.1	3.4	0.7	4857	17 d	Cohort W
2	38	Never	In ₂ O ₃	19 y	Pneumo-thorax	Left upper lobe	VATS	Apical bulla: 12.8, Mediastinal side bulla: 2.6	7.7	3.1	2484	0 d	Cohort W
3	62	Never	ITO	4 y 11 mo	LC	Right upper lobe	VATS	Anterior: 31.2	31.2	7.7	4052	0 d	Cohort W
4	40	Former	ITO	14 y	IP, mild PE	Right lobe	VATS	Upper anterior: 111.3, Lower superior 169.2, Lower posterior basal: 38.4	106.3	35.5	2994	2 mo	Cohort W
5	55	Former	ITO	13 y 4 mo	Severe PE, IP, pulmonary hypertension	Bilateral lobe	Bilateral lung transplantation	Right: Upper posterior: 53.8, Middle medial: 168.0, Lower posterior basal: 211.2 Left: Upper apical-posterior: 154.9, Upper lingular: 206.5, Lower lateral-posterior basal: 172.8	161.2	60.4	2669	8 d	Cohort W
6	31	Never	In ₂ O ₃ In(OH) ₃	5 y	IP, PE	Left lobe	VATS	Upper apical-posterior and lower superior mixture: 17.4	17.4	70.5	247	9 d	Ref No. 8

Note: In-L: Arithmetic mean of indium in the exenterated lung tissue ($\mu\text{g/g}$ wet weight). In-S: Indium in serum (ng/mL). Lag: Time gap between samplings of lung tissues and blood. Cohort W: Worker in our cohort study.

Abbreviations: IP, Interstitial pneumonia; ITO, Indium-tin oxide; LC, Lung cancer; PE, Pulmonary emphysema; VATS, Video-assisted thoracic surgery.

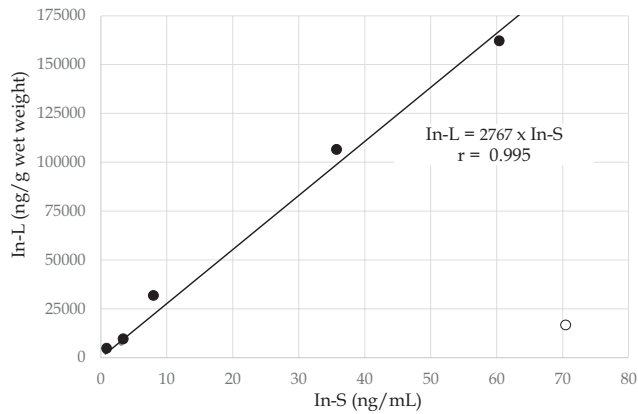


FIGURE 1 Relationship between In-S and In-L. Closed circle (●): Cases 1-5. Open circle (○): Case 6

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DISCLOSURE

Approval of the research protocol: The cohort study in which Cases 1-5 participated was approved by the Kyushu University Certified Institutional Review Board for Clinical Trials (approval number 30-69), and by the Ethics Committee of the School of Medicine, Keio University (approval number 20 110 268). *Informed Consent:* Written informed consent for using epidemiological and clinical data were obtained from Cases 1-5 after showing his own data to each case. *Registry and the Registration No. of the study/trial:* N/A. *Animal Studies:* N/A.

CONFLICT OF INTEREST

The authors declare no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

HM and TA contributed to the management between the patients and doctors. HM takes responsibility for the integrity and accuracy of the data. HM and OK analyzed the data and wrote the primary draft of the article. TA and NM assisted in the interpretation of data and to critical revision of the manuscript. All authors approved the final version of the manuscript.

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