

THREE CASES OF THINNER-SNIFFING AND ESTIMATING THE FATAL CONCENTRATION OF TOLUENE BY TOXICOKINETICS

Tatsuya HOBARA, Masayuki OKUDA, Masayuki GOTOH, Kouichi OKI, Hiroyuki SEGAWA, Ichiro KUNITSUGU

Department of Public Health, Yamaguchi University School of Medicine, Ube, Japan

ABSTRACT: To determine the potentially lethal level of thinner concentration in the air, we measured the concentration of toluene in the blood and other media of three patients who suffered severe acute thinner intoxication between 4 January 1996 and 21 April 1997 in Ube city. The concentration of toluene in blood were 30.2 mg/l in dead patient, and 13.7 mg/l and 17.5 mg/l in recovered patients, respectively. By extrapolation from the results of our previous toxicokinetic research on toluene poisoning in anesthetized dogs, the fatal concentration of toluene was estimated to be approximately 1800 to 2000 ppm over a one-hour exposure.

KEY WORDS: Toluene; Toxicokinetics; Hippuric acid.

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INTRODUCTION

Toluene is a solvent commonly used in paint, plastic, and printing, as well as in other industrial environments. In humans, there is a well-documented, dose-dependent relation between the concentration of toluene in inhaled air and that in blood [4, 7, 10]. A strong correlation in humans exists between the toxicity of toluene and the concentration of toluene in inhaled air. The acute neurotoxic effects of toluene increase in severity from mild headache at low doses (50 ppm) to muscular weakness, nausea, and impaired coordination at high doses (100 to 200 ppm). Acute intoxication due to ingestion of excessive amounts is unusual but often fatal [1, 3, 8, 12, 13]. Since 1996, we have encountered only a few patients who have become severely ill due to working with paint thinner while painting in a building or other workplace in Ube city. Ube Civil Defense Force ambulance teams brought these patients to the Accident and Emergency Department of Yamaguchi University Hospital where they were treated by various procedures. At the time of admission, among many laboratory investigations performed, we measured the concentrations of toluene in blood and those of toluene and hippuric acid in urine of the patients. In our previous study of anesthetized dogs [6], we examined the concentration of toluene in expired air, and in arterial and venous blood. The concentrations were de-

terminated repeatedly during and after toluene exposure. Using the data of that study, we used toxicokinetics research methods to estimate the fatal levels of toluene in ambient air over certain exposure periods.

WORK CONDITIONS AND MEDICAL TREATMENT

We present three cases of thinner toxicosis in the workplace. All patients were men. One died 3 days after the crisis that brought him to the emergency department. The other two recovered and had no aftereffects. Patient A (age 22) was working as a painter and using thinner while painting the wall and ceiling of a small room in a building that consisted of a number of independent businesses. Figure 1 shows the floor plan of the room. Two exhaust fans were provided in the room, one above the gas range and the

Fig. 1. The floor plan of the room where patient A and C worked.

Fig. 2. A rough sketch of the channel where patient B worked.

other in the lavatory, and both were small and weak. At the time this patient entered the hospital, he was unconscious, and he died 2 days later despite intensive treatment. The treatment included intravenous drips containing vitamins B₁, B₆, C and E, steroid, digitalis, antibiotics and oxygen inhalation through tracheal intubation. Patient B (aged 53) also worked with paint thinner in a discharge channel of a chemical factory. A rough sketch of the channel is shown in Figure 2. While painting in the channel, he felt unwell and fell to the ground about 6 M from the entrance. He was conscious, however, and was brought promptly to the above hospital. After 3 days of standard treatment for toluene poisoning in the hospital, he recovered and suffered no permanent damage. Patient C (aged 39) worked with paint thinner in a building similar to that described above. The room ventilation was about the same as that shown in Figure 1. He lost consciousness while painting in a small room, was found by his fellow workers, and was transported promptly to the above hospital. After 2 days of treatment, he regained consciousness. One week later, he was discharged from the hospital with no aftereffects.

MATERIALS AND METHODS

Laboratory investigations of blood were conducted with an autoanalyzer (Hitachi 7250, Hitachi Ltd, Tokyo, Japan). The toluene concentrations in the blood and urine were determined by gas chromatograph/mass spectrometry (GC/MS) (HP5972, Hewlett Packard Co. Palo Alto CA). Hippuric acid concentration in the urine was measured with a KKLC Module (Waters Co. Yamagata Japan). The analytical methods used were reported previously [11]. Laboratory investigations included the following:

1. for peripheral blood – red blood cells, white blood cells, platelet, hemoglobin, and hematocrit;
2. for liver and pancreas functions – total protein, albumin, globulin, alkaliphosphatase, aminotransferase (AST) and aspartate aminotransferase (ALT), γ -GTP, bilirubine, and amylase;
3. for renal function – urea nitrogen and creatinine in serum, sugar, protein, and blood in urine;
4. for toluene and its metabolites – toluene in urine and blood, hippuric acid in urine.

TABLE I. LABORATORY INVESTIGATIONS OF THREE PATIENTS

(I) Biochemical analysis in blood				
Item	Normal range	Patient A (22)	Patient B (53)	Patient C (46)
RBC	450~550 x 10 ⁴ / μ l	461/ μ l	493/ μ l	503/ μ l
WBC	4000~10000 x 10 ⁴ / μ l	9600/ μ l	8800/ μ l	7600/ μ l

PLT	15~40 x 104/ μ l	19.2/ μ l	20.0/ μ l	16.3/ μ l
TP	6.8~8.7 g/dl	6.7 g/dl	5.9 g/dl	6.1 g/dl
T-Bil	0.3~1.2 mg/dl	0.5 mg/dl	0.9 mg/dl	0.7 mg/dl
Alb	3.7~4.7 g/dl	3.9 g/dl	3.4 g/dl	3.6 g/dl
Glo	3.1~3.6 g/dl	2.8 g/dl	2.5 g/dl	2.8 g/dl
Al-P	114~358 IU/l	114 IU/l	209 IU/l	151 IU/l
UN	8~23 mg/dl	10 mg/dl	10 mg/dl	13 mg/dl
CRE	0.64~1.12 mg/dl	1.20 mg/dl	0.73 mg/dl	1.02 mg/dl
GOT	12~34 IU/l	577 IU/l	29 IU/l	76 IU/l
GPT	5~43 IU/l	397 IU/l	30 IU/l	62 IU/l
γ -GTO	12~80 IU/l	43 IU/l	46 IU/l	98 IU/l
CRP	0~0.25 mg/dl	0.16 mg/dl	0.22 mg/dl	0.15 mg/dl
AMY	32~98 IU/l	98 IU/l	96 IU/l	86 IU/l
(II) Toluene concentration [μ g/l]				
Blood	0	30213	13707	17513
Urine	0	850	149	265
(III) Hippuric acid concentration [g/l]				
Urine	0.3~0.6	2.23	3.11	4.31

RESULTS AND DISCUSSION

Table I shows the data from the laboratory investigations of the three cases of thinner intoxication. AST and ALT levels in patient A were extremely high, and their values in patient C were moderately high; however, they were within the normal range in patient B. The γ -GTP values was high in patient C, but within normal range in patients A and B. Other laboratory data were within normal ranges in all three patients. The physical findings for patient A included heart rate of 120 beats/min, blood pressure at 76/42 mm Hg, respiratory distress, rales on auscultation, severe muscle weakness, absence of deep tendon reflexes, and stupor. A chest X-ray revealed areas of atelectasis and bilateral pleural effusion. On ECG, voltages were depressed in all derivations, indicating myocardial damage. On admission, patient B was conscious with a blood pressure of 136/74 mm Hg, pulse rate of 75/min, and respiratory rate of 21/min. Neurological examination showed no localization profile. Examination of heart, lungs and abdomen showed no abnormalities, and no unusual signs were noted on ECG or chest X-ray. Patient C was found conscious but disoriented. His initial blood pressure was 126/71

mmHg, pulse rate was 98/min, and respiratory rate was 23/min. His ECG and chest X-ray were normal, and no abnormalities were detected during physical examination.

When toluene concentrations in the blood and urine were measured, significant differences were found between patients A and patients B and C in the blood levels ($p < 0.05$). In patient A, toluene concentrations were 30.2 mg/l in blood and 0.15 mg/l in urine. In patient B and C, the concentrations were 13.7 mg/l and 17.5 mg/l respectively in blood and 0.15 mg/l and 0.26 mg/l respectively in urine.

The toxicokinetics model of toluene that was conducted using anesthetized dogs in our laboratory was applied to the data from these patients [6]. In this previous study, the absorption of toluene within 1 hour of exposure was 25, 56, and 74 mg/kg at 700, 1500 and 2000 ppm respectively (absorption ratio = 27%). At the same time, the toluene concentration in venous blood was 27, 56 and 67 mg/l at 700, 1500 and 2000 ppm respectively. One hour after the end of exposure, the concentrations were 10, 18, and 25 mg/l at 700, 1500 and 2000 ppm, respectively. The volume remaining one hour after the end of exposure was 37% of the original uptake.

In the present study, we estimated that it took about one hour to transport the patients to the hospital and draw blood. Over this period, patient A became severely weakened and showed decreased respiratory volume. For this reason, we estimated his respiratory volume at a half of normal respiration and calculated his remaining uptake volume to be about 70% one hour after the end of exposure. In contrast, patients B and C had normal respiration by one hour after exposure and their remaining uptake ratios were estimated at about 37%. Using these remaining uptake percentages and the experimental data obtained from our previous study, we calculated the uptake volumes of toluene in these patients. In this study, absorptions of toluene in patient A, B and C were approximately 65, 40 and 52 mg/kg, respectively. We also calculated the exposure concentration over one hour periods: that of Patient A was approximately 1800 to 2000 ppm; that of patient B was 1000 to 1300 ppm, and that of patient C was 1400 to 1600 ppm. Nomiya et al. reported the fatal concentration of toluene to be approximately 2000 ppm with a 30 minutes exposure [9]. In another study, Batchelor and Fairchild [2, 5] reported these values to be at 1600 to 4000 ppm at a one hour exposure in rat experiments. From these reports and our previous data, we propose that the fatal concentration of toluene in humans is approximately 1800 to 2000 ppm over about a one hour exposure period.

The toluene concentrations in urine were very low compared to those in blood, but urine concentrations were proportional to those found in blood. This relationship indicates that urinary concentration of toluene is a good index of toluene exposure and is useful for biological monitoring of acute toxic exposure.

The concentrations of urinary hippuric acid in patients A, B, and C were 2.23 g/l, 3.11 g/l and 4.06 g/l, respectively. Hippuric acid levels were not directly affected by the uptake volume of toluene. Patient A had serious liver damage, and his ability to metabolize toluene was impaired. In addition the hippuric acid concentrations were very low compared to the toluene uptake volumes in these patients [10]. We do not have an explanation for this phenomenon. In future studies, we plan to investigate further the is-

sues concerning the best method for measuring toluene exposure and the concentration/time parameters involved in potentially fatal exposure.

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