LETTERS TO THE EDITOR

A Case of Thinner Sniffing: Part 2. Urinary Excretion of Cresols and Methanol after Inhalation of Toluene and Methanol

Key words: Thinner sniffing—Toluene—Methanol—Hippurate—Cresols—Urinary excretion

In the previous letter, we reported a case of recurrent sniffing of toluene and methanol, and discussed the relationship between neuro-psychological symptoms and urinary findings¹⁾. As the patient has neither complained of visual disturbance nor been diagnosed with optic nerve alteration, which is well-known sequela of methanol poisoning, we were interested in the urinary excretion of methanol and in the metabolism of toluene in this patient. In the present study, we analyzed urinary metabolites of toluene: hippurate and cresol isomers^{2,3)} and methanol.

The patient: a 32-year-old man was admitted to our university hospital twice in 1985 after inhalation of thinner, a solvent mixture of toluene and methanol. Estimated inhalation levels were 3,067 ppm and 12,350 ppm for toluene and methanol respectively¹⁾. Urine samples were collected at each urination during admission and stored in a cold room at 4°C until the analysis of hippurate was possible. For the analysis of cresols and methanol, a portion of each urine specimen was transferred into individual air-tight vials and kept in a freezer at -20°C until the analyses were commenced. Urinary hippurate was measured by the HPLC method using the C18 column as described by Ogata *et al.*⁴⁾. Cresol isomers and methanol were analyzed using GC methods. The columns used were KG-02 for cresol isomers as described by Kawai and Horiguchi⁵⁾ and 10% SBS 100 on Shimalite TPA for methanol as described by Kawai *et al.*⁶⁾.

Figures 1 and 2 show the urinary excretion of hippurate and methanol, and cresol isomers respectively. The maximum excretion rates of these substances were observed within 500 min after final sniffing and decreased exponentially in a linear manner up to 3000 min. There have been few reports concerning visual disturbance after inhalation of methanol rather than ingestion. Takeuchi reported a rare case of methanol poisoning with optic nerve alteration in a female worker who suffered low level exposure (200 ppm over 6 months), and he suggested the possibility of individual differences in the susceptibility to methanol⁷⁾. In the case of methanol poisoning after ingestion, Roe concluded that a cause of amblyopia and amaurosis in humans was uncompensated acidosis, triggered by the presence of formic acid⁸⁾. In the present case, no acidosis was observed during admission. In cases of fatal methanol poisoning by ingestion, Lund reported that the

Fig. 1. Urinary excretion of hippurate and methanol after thinner sniffing
 HA: hippurate, ME: methanol.
 Open (○) circle: 1st admission, solid circle (●): 2nd admission.

*: logarithmic mean and standard deviation of excretion rates during the period from 3830 to 7480 min and from 3980 to 6290 min for the 1st and 2nd admissions respectively.

Fig. 2. Urinary excretion of cresol isomers after thinner sniffing

O: o-cresol, M: m-cresol, P: p-cresol.

Open (○) circle: 1st admission (●) circle: 2nd admission.

*: logarithmic mean and standard deviation of excretion rates during the period from 3830 to 7480 min and from 3980 to 6290 min for the 1st and 2nd admissions respectively. In the case of m-cresol (M), there was only one observation recorded as the remainder were under the detection limit ($<0.2 \text{ mg/l}$).

Table 1. Biological half-lives of hippurate, cresols and methanol in the present case.

Urinary component	Biological half-life (min)	Post-inhalation period* (min)	Maximum excretion rate* (observed period: min)	Admission
Hippurate	730	420—2990	23.7 mg/min (420—605)	1
	704	— 50—3010	12.7 (— 50—180)	2
o-Cresol	690	420—2990	15.3 μ g/min (420—605)	1
	623	— 50—3010	11.9 (— 50—180)	2
m-Cresol	787	420—2990	11.6 μ g/min (420—605)	1
	887	315—3010	3.7 (315—510)	2
p-Cresol	1956	420—2990	199.5 μ g/min (420—605)	1
	912	— 50—3010	75.5 (315—510)	2
Methanol	350	420—2990	226.7 μ g/min (420—605)	1
	318	— 50—1865	183.7 (180—315)	2

Half-lives were calculated from results illustrated in Figs. 1 and 2.

* : after the end of inhalation. (—) indicates previous urination was before the end of inhalation.

methanol level in urine ranged from 1400 to 2400 mg/l⁹⁾, which is about 10 times higher than that in the present case (200–230 mg/l). On the other hand, Leaf and Zatman measured 7.8–25.6 mg/l methanol in urine during experimental inhalation of methanol at 476.6–1092.5 ppm for 150 min, and no visual disturbances were observed¹⁰⁾. A proportional relationship observed between the level inhaled and that excreted in urine is used in the biological monitoring of methanol exposure; both the methanol inhaled (12000 ppm) and its level in urine (200–230 mg/l) are about ten times higher than those in the experiment by Leaf and Zatman.

Table 1 shows biological half-lives of the metabolites of toluene, and methanol. Hippurate excretion was prolonged about 6 times that after experimental exposure to 100–200 ppm toluene (74–117 min)^{11,12)}. Although a correlation between inhaled level and urinary level was observed, methanol excretion was also prolonged about 3 times that calculated from experimental exposures to 35–210 ppm methanol (90–180 min)¹³⁾; A long retention time of methanol might relate to the prolonged neuro-psychological symptoms in the present case, as the urinary methanol level reflects directly to the level in blood. From the above observation, we suspected a metabolic interaction between toluene and methanol, since these two chemicals are metabolized by common enzymes: alcohol-and aldehyde-dehydrogenases¹⁴⁾. The main metabolic pathway of toluene in humans is side chain oxidation through benzyl alcohol, benzaldehyde and benzoate which is a precursor of hippurate¹⁵⁾, and that of methanol is through formaldehyde to formic acid¹⁶⁾. If an interaction occurred during this process, excretion of unmetabolized methanol from the body might be increased. Prolonged excretion of methanol in the present case might provide support for the existence of this interaction,

Table 2. Correlation of hippurate and o-cresol in urine and comparison of values between measured and estimated o-cresol levels.

After exposure (min)	Measured hippurate (X) (g/l)	Estimated o-cresol (Y) by			Measured o-Cresol (Z) (mg/l)
		Equation A (mg/l)	Equation B (mg/l)	Equation C (mg/l)	
180 (Z-Y)	21.80	18.9 (+48.1%)	10.8 (+159.3%)	6.7 (+316.7%)	28.0
315 (Z-Y)	4.75	3.5 (+14.3%)	2.4 (+66.7%)	1.7 (+131.2%)	4.0
510 (Z-Y)	21.51	18.6 (+7.5%)	10.7 (+86.9%)	6.6 (+201.2%)	20.0
605 (Z-Y)	24.40	21.2 (-25.9%)	12.1 (+29.8%)	7.5 (+109.9%)	15.7
1270 (Z-Y)	19.33	16.7 (-15.6%)	9.6 (+46.9%)	6.0 (+135.0%)	14.1

A : $Y = 0.904X - 0.814$, $n = 14$, $r = 0.9093$, at 0–2535 min.

B : $Y = 0.496X - 0.002$, $n = 27$, $r = 0.8992$, at 2720–9860 min.

C⁽¹⁷⁾ : $Y = 0.293X + 0.334$, $n = 74$, $r = 0.7036$, before and at 0–44h after exposure to 200 ppm toluene. 17) Woiwode and Drysch (1981)

Z-Y : (measured level-estimated level)/estimated level $\times 100$ (%)

however, we analyzed neither formaldehyde nor formate. In the case of toluene metabolism, if the main pathway was interrupted, an alternative pathway to cresols through the MFO system might be increasingly utilized. In order to examine the above hypothesis, we calculated the regression equation between hippurate (X) and o-cresol (Y) and estimated levels of o-cresol excreted in urine in the early stages of end-exposure. Table 2 shows the results of this analysis. Equations A and B were obtained from data from urinalysis between 0 to 2535 min and from 2720 to 9860 min after the exposure, respectively. Ortho-cresol level measured at 180 min after the end of exposure was higher than the level estimated using the given equations, being increased by 48.1% or 159.3%. Comparison of these results with the levels expected using the equation given by Woiwode and Drysch relating to exposure to 200 ppm toluene for 4 h⁽¹⁷⁾, the present result showed a far higher urine level of o-cresol. The above observation suggests at least two possibilities: a metabolic interaction and/or limitation of urinary excretion of hippurate through the kidney due to an excessive dose of toluene.

From another point of view, individual differences in the activity of alcohol- and aldehyde-dehydrogenases have been pointed out in relation to genetic background⁽¹⁸⁾. However there have been no reports concerning the relationship between methanol poisoning and genetic basis, especially in workers dealing with alcohol-containing solvents. This is an interesting point for future discussion.

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