Urinary Thiodiglycolic Acid Levels for Vinyl Chloride Monomer-Exposed Polyvinyl Chloride Workers

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Thiodiglycolic acid (TdGA) is the major metabolite of vinyl chloride monomer (VCM) detected in human urine. Although urinary TdGA has been reported to be associated with ambient VCM exposure, the relationship between urinary TdGA and a low level of air VCM is not clear. Questionnaires were administered to 16 polyvinyl chloride manufacturing workers to obtain a detailed history of occupation and lifestyle. For each worker, personal air monitoring for VCM was performed and a time-weighted average for VCM exposure was calculated. The urinary TdGA levels at the end of a work shift, and at the commencement of the next shift, were also assessed for each worker. Urine analysis revealed that TdGA levels at the beginning of the next shift were higher than those at the end of that shift. Workers experiencing a VCM exposure greater than 5 ppm in air revealed a urinary TdGA level significantly greater than those experiencing a VCM exposure of less than 5 ppm ($P < 0.05$*). The best fit of regression for urinary TdGA on air VCM was* $Y = 1.06 + 0.57X$ *for urine collected at the commencement of the following work shift, where X is the air VCM concentration and Y is the urinary TdGA concentration (*$r^2 = 0.65$, $P < 0.01$*). We conclude that the urinary TdGA level is best detected at the commencement of the next shift and that it can be used as an exposure marker for polyvinyl chloride workers when the air VCM level to which they are exposed is greater than 5 ppm.* (J Occup Environ Med. *2001;43:934–938*)

Vinyl chloride monomer (VCM) exposure has been associated with angiosarcoma of the liver and is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC).[1] To protect VCM-exposed workers from developing diseases associated with their VCM exposure, the environmental VCM level to which they are (occupationally) exposed is periodically monitored to ensure that the air concentrations are below permissible levels.[2] Environmental monitoring, however, may not reflect the actual worker exposure level because of differences in VCM levels for individual workers. To measure the actual dose of VCM absorbed by a worker, methods to detect urinary TdGA, a major metabolite of VCM in human urine, have been developed.[3–6] Although a VCM-exposed worker's urinary TdGA level has been reported to be associated with his or her air VCM exposure level, these studies have focused on the procedures necessary for detecting the presence of TdGA in urine, and they provide limited information in terms of study design.[7,8] Thus, the most appropriate time to detect urinary TdGA subsequent to VCM exposure for humans remains clear. Furthermore, the exact relationship between urinary TdGA level and air VCM concentration must be resolved, particularly with regard to low levels of VCM.[8,9] We conducted a comprehensive study to investigate the relationship between air VCM and urinary TdGA levels over a pe-

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riod of time for workers exposed to low levels of VCM. Some potential confounders for urinary TdGA level were also evaluated.

Materials and Methods

Study Population and Measurement of Air VCM Level

A total of 16 male workers were enrolled from two Taiwanese polyvinyl chloride manufacturing plants. Personal sampling was conducted to obtain VCM exposure information using a modification of a method (#1007) originating from the National Institute for Occupational Safety and Health.[10] Personal air sampling conducted in workers' breathing zones for 6 to 7 hours during work shifts was performed. At the completion of monitoring, all samples were immediately capped and stored at 4°C. The sample-contained VCM was subsequently extracted with carbon disulfide and analyzed by gas chromatography with mass spectrometry. The air VCM time-weighted average for each worker was calculated.

Epidemiological Information

After providing informed consent, each subject was surveyed by an interviewer-administered questionnaire to obtain information pertaining to smoking activity, alcohol consumption, medication taken, and medical and occupational histories. A detailed occupational history was compiled for each study subject, including job title, daily activity within 1 week of sample collection, and information regarding whether or not it was normal practice for the worker to use a respirator while working. Current smokers were defined as those who had smoked within a period of 6 months before sample collection. Alcohol drinking was defined as consuming alcohol at least once per week.

Urinary TdGA Measurement

Urine samples from the 16 participating workers were collected at the end of a work shift and at the commencement of the next shift. Urine collected at the end of a shift was collected approximately 7 to 8 hours subsequent to the start of exposure; and urine collected at the beginning of the following shift was collected approximately 24 hours after the start of exposure. Urine samples were stored at −20°C until used for analysis. Five milliliters of collected urine was mixed with H_2SO_4 and NaCl, after which ethyl acetate was added and the mixture was centrifuged. The supernatant was subsequently transferred to another tube to dry. Following this, 400 μL of pyridine and 800 μL of *N*, *N*-diethyltrimethylsilyamine were added to the tube containing the dried supernatant to achieve silylation, after which gas chromatography/mass spectrometry was used to determine the concentration of TdGA derivatives in the samples. Urinary TdGA concentration was adjusted for urinary creatinine level. For those specimens demonstrating a urinary TdGA level below the detectable level (1 mg/L), a notional TdGA level equal to one-half of the detection limit adjusted by urinary creatinine was assigned.

Statistical Analysis

Statistical Analysis System (SAS™) software was used for the statistical analysis. The Wilcoxon test was used to test differences in urinary TdGA level by sampling time and exposure groups. Regression of urinary TdGA level on air VCM concentration was also performed and tested for urine collected at the commencement of the following shift. Subsequently, a multiple regression model was used to determine if any potential variables were associated with urinary TdGA level at the beginning of the following shift after adjusting for the air VCM.

TABLE 1
Basic Characteristics of the Study Subjects

Variables	Total (n = 16)	
	n	%
Age (yrs)		
>40	9	56
≤40	7	44
VCM exposure*		
High	4	25
Moderate	6	37.5
Low	6	37.5
Duration of Employment (yrs)		
>15	9	56
≤15	7	44
Smokers†		
Yes	10	63
No	6	37
Alcohol drinkers‡		
Yes	7	44
No	9	56
Tea drinkers		
Yes	7	44
No	9	56
Coffee drinkers		
Yes	5	31
No	11	69

* VCM, vinyl chloride monomer. Exposure: high > 5 ppm; 1 ppm ≤ moderate ≤ 5 ppm; low < 1 ppm.

† Smoking: smoking within 6 months of sample collection.

‡ Drinking: alcohol consumption ≥ 1 occasion per week.

Results

Study Population and Exposure Level of VCM

Sixteen male workers were included for the analysis. The basic characteristics of the study population are summarized in Table 1. The mean age of these workers was 44 years; mean duration of employment was 19 years. Using our definitional criteria listed above, approximately 43.8% of workers consumed alcohol at least once each week, and 68.5% of workers were current smokers.

Urinary TdGA and (personal) air VCM levels for each study subject are depicted in Table 2. Workers undertaking tank-cleaning activities exhibited a (personal) air VCM exposure level ranging from 0.05 to

TABLE 2
TdGA Level in Urine by VCM Level in Air and Sampling Time for Study Individuals*

Subject	Job Title	VCM in Air (TWA, ppm)	TdGA in Urine (mg/g Cr)	
			End of Shift	Start of Next Shift
1	Tank cleaner	0.05	16.00	3.90
2	Tank cleaner	0.10	2.20	1.70
3	Tank cleaner	0.17	2.10	1.90
4	Stripper operator	0.25	0.82†	0.47†
5	Polymerization operator	0.58	2.10†	0.42†
6	Foreman	0.68	0.28†	0.36†
7	Polymerization operator	1.11	2.70	2.50
8	Supervisor	2.23	1.50†	2.50
9	Tank cleaner	2.91	5.70	21.00
10	Operator for wastewater	3.39	2.40†	0.32†
11	Polymerization operator	4.03	14.00	2.90
12	Tank cleaner	4.86	1.10†	4.00
13	Operator for material adding	5.59	3.60	6.20
14	Recovery operator	8.17	1.60†	2.90
15	Polymerization operator	12.08	3.70	6.00
16	Polymerization unloading	13.38	14.00	12.00

† Nondetectable: Urinary TdGA is calculated as one-half of the detection limit (1 mg/L)/urinary creatinine (g/L).

* TdGA, thiodiglycolic acid; VCM, vinyl chloride monomer; TWA, time-weighted average; ppm, parts per million; Cr, creatinine.

4.86 ppm. Machine operators in the polyvinyl chloride-polymerization area revealed a VCM exposure level ranging between 0.58 and 13.38 ppm. Stripper operators demonstrated a mean air VCM exposure level of 0.25 ppm, and recovery operators experienced a mean level of 8.17 ppm. Operators of wastewater treatment were exposed to a mean air VCM level of 3.39 ppm, whereas foremen and supervisors experienced VCM exposure ranging from 0.68 to 2.23 ppm. Study subjects were also classified into high-, moderate-, and low-exposure groups by using 1 and 5 ppm VCM exposure as cutoff points. The low VCM-exposure group ($n = 6$) included foremen, tank cleaners, and operators of polymerization and stripping equipment. The moderate VCM-exposure group ($n = 6$) included operators for polymerization and wastewater-management equipment, a supervisor, and several tank cleaners. The high VCM-exposure group ($n = 4$) included operators of polymerization, material adding, and unloading and recovery equipment.

Urinary TdGA Concentration and VCM Exposure

The urinary TdGA level collected at the commencement of the following shift was greater than that collected at the end of that shift for the high-exposure group, although the difference was not statistically significant. This pattern was not observed for the low-exposure and moderate-exposure groups, in which the urinary TdGA level collected at the beginning of the following shift was not greater than that collected at the end of that shift (Fig. 1). For urine samples collected at the commencement of the following shift, urinary TdGA level was significantly greater for subjects from the high-exposure group than for subjects in the moderate-exposure and low-exposure groups ($P < 0.05$, Wilcoxon test). Urinary TdGA levels did not differ between the moderate-exposure and low-exposure groups. When data for the outlier (subject #9, a tank cleaner) was excluded, the above results remain. The subsequent analysis was focused on the TdGA of 15 subjects. The best fit of the regression of urinary TdGA on air VCM was: $Y = 1.06 + 0.57X$ for urine collected at the beginning of the following shift, where X is the air VCM concentration, and Y is the urinary TdGA concentration ($r^2 = 0.65$, $P < 0.01$) (Fig. 2). Again, when subjects who exhibited a urinary TdGA level below detection limits were excluded from the study, similar results were obtained ($r^2 = 0.63$, $P < 0.01$).

Further analysis using urinary TdGA collected at the commencement of the following shift and potential confounders, including participant age, smoking habits, and alcohol consumption, were tested in a multiple regression model. None of these factors was found to be associated with urinary TdGA level.

Discussion

The concentration of TdGA in urine collected from workers at the commencement of the following shift was greater than that collected at the end of the shift for the high-exposure group. Previous investigation has indicated that urinary TdGA levels for VCM-exposed workers reach their peak in the period between the completion of one shift and the beginning of the next shift,[9] and our current findings are consistent with this. We thus suggest that the optimal time for collecting workers' urine samples for biological monitoring of VCM exposure is at the commencement of the next shift. A similar observation was not made for workers exposed to atmospheric VCM at a level below 5 ppm because of confounding by existing background TdGA levels.

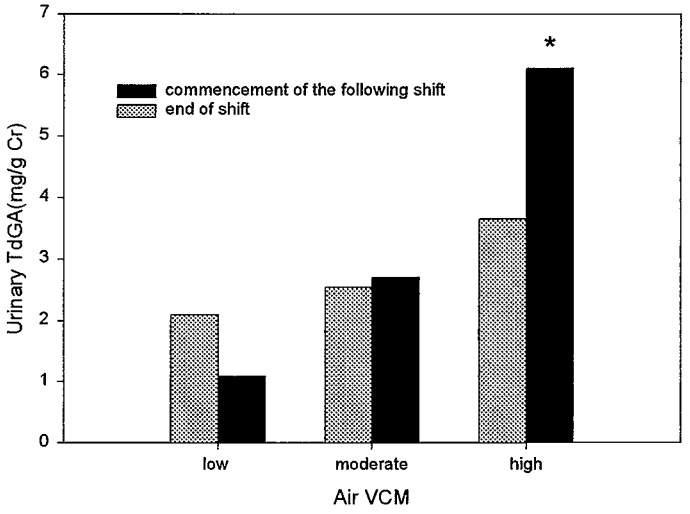

Fig. 1. Urinary TdGA by air VCM and urine collection time. * $P < 0.05$, urinary TdGA in the high-exposure group compared with that in the moderate-exposure and low-exposure groups.

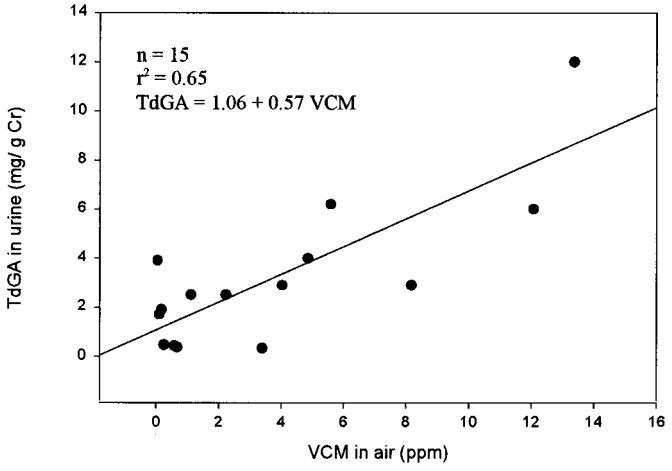

Fig. 2. VCM in air versus TdGA in urine at the commencement of the following shift.

For workers in the high-exposure group, the concentration of TdGA in urine collected at the beginning of an upcoming shift was greater than that for subjects in either the moderate-exposure or low-exposure groups. An air VCM exposure level of between 1 and 5 ppm, however, did not seem to elicit a significantly greater urinary TdGA level than for an air VCM exposure level below 1 ppm. Studies pertaining to the association between urinary TdGA levels and low-level environmental exposure are not consistent with regard to their conclusions. One study reported that a group of workers experiencing an air VCM exposure at a level between 0.3 and 10 ppm reflected a greater (not statistically significantly) mean urinary TdGA level as compared with a control group.[8] Another study reported that compared with controls, the urinary TdGA level was greater for VCM-exposed workers when the air VCM level was between 1 and 5 ppm.[9] These two studies, however, were not intended to elucidate the relationship between air VCM levels and urinary TdGA levels. Using a comprehensive experimental design, we found that urinary TdGA levels increased with increasing VCM exposure when the air VCM level was above 5 ppm. A previous study also revealed that the urinary TdGA level was an unreliable indicator for VCM vapor when the air VCM level was below 5 ppm.[11] We concur with this study, and we conclude that when the air VCM concentration is below 5 ppm, urinary TdGA may not be reliably used as an individual reference for VCM exposure.

Our study did not find that lifestyle, including smoking, alcohol consumption, and tea and coffee drinking, were associated with TdGA. One study reported that alcohol consumption increases TdGA excretion for VCM-exposed workers[7]; however, alcohol consumption by subjects in our study was relative low. Further study is required to clarify the influence of alcohol consumption on the concentration of TdGA in urine.

A potential deficit in the current study is that a number of urinary TdGA levels were below the analytical detection limits, presumably because the corresponding air VCM levels were also relatively low, given current occupational health guidelines for a safe work environment. Further development of methods for the analysis of specific urinary metabolites of VCM is needed, particularly when air VCM levels for most workers are below 5 ppm.

Acknowledgments

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More Facts

- Number of pages related to the Iran–Contra investigation that are still sealed: 4,630,000.
- Ratio of the number of pardons granted by President Clinton to the number granted by President Reagan: 1:2.
- Ratio of the number of pardons granted by President Reagan to the number granted by President Eisenhower: 1:3.
- Percentage of TV investigative reporters and editors who say that an advertiser tried to kill one of their stories: 60.
- Average age at which Americans believe their physical attractiveness peaks: 38.
- Percentage of US adults who are at least “somewhat satisfied” with their physical appearance: 88.
- Length of an ID microchip that Singapore now implants in the necks of all imported dogs: 13 mm.
- Minimum number of Las Vegas casinos that use face recognition to identify cheats: 25.
- Factor by which the cost of China’s Three Gorges dam will exceed its original $4.5 billion budget: 16.

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