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Early Detection and Signs of Hepatoangiosarcoma Among Vinyl Chloride Workers

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Health examinations of 108 workers exposed to vinyl chloride monomer (VCM) at a Japanese chemical plant were carried out in 1979. The polymerization of vinyl chloride was started at the plant in 1949. In this study, the highest concentration of VCM in autoclaves was determined to be 250 ppm in 1961. However, the workers at the plant had been exposed to higher concentrations of VCM several times before 1960. More recent VCM exposure was considered negligible. Examinations assessed data on age, height, weight, obesity index, sake consumption, VCM exposure concentration, latent period, cumulative exposure, ICG (indocyano green test), serum bilirubin, GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transminase), A1-P (alkaline phosphatase), GGT(γ-glutamyl transpeptidase), ZTT (zinc turbidity test), LDH (lactate dehydrogenase), cholesterol, TTT (thymol turbidity test), A/G (albumin globulin ratio), and thrombocytes. Variation in VCM exposure did not affect (1) tests of pigment excretion from the liver, such as ICG; (2) thrombocytes; and (3) enzyme activity (such as GPT); nor bilirubin or flocculation reaction in serum.

Key words: vinyl chloride monomers, liver function tests, ICG, thrombocytes

INTRODUCTION

Many studies [Block, 1974; Creech and Johnson, 1974; Nicholson et al, 1975; Waxweiler et al, 1976; Bertazzi et al, 1980] of workers exposed to vinyl chloride monomer (VCM) that reported a high incidence of hepatoangiosarcoma were reviewed. Some investigators [Marsteller et al, 1975; Popper and Thomas, 1975; Veltman et al, 1975] considered that portal hypertension among the workers could be regarded as a precursor of hepatoangiosarcoma. Early diagnosis of hepatoangiosarcoma has been studied [Krammer and Mutchler, 1972; Veltman et al, 1975; Wyatt et al, 1975; Bertazzi et al, 1980], but definitive approaches to diagnosis have been elusive.

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We investigated liver function of workers exposed to VCM at a Japanese chemical plant. Hepatoangiosarcoma was not found among them, and no statistically significant differences in mortality rate were detected between the VCM-exposed workers and a control group [Masuda, 1980]. No VCM-exposed workers were shown to suffer from liver dysfunction. Statistical analyses, including multivariate analyses of liver function data, were carried out and early diagnosis of liver dysfunction among VCM workers was sought.

METHODS

In 1979, health examinations of 108 workers who had been exposed to VCM since 1949, at a Japanese chemical plant, associated with the polymerization of vinyl chloride monomers [Masuda, 1980], were carried out. The highest concentration of VCM in the autoclaves was recorded as 250 ppm in 1961. However, the workers had been exposed to considerably higher concentrations several times before 1961 [Masuda, 1980]. Since the plant design was improved and workers were no longer required to service the autoclaves, the concentration of VCM in the working environment has become undetectable and recent exposure to VCM is considered negligible.

Health examination included the following: age (years), height (cm), weight (kg), obesity index, sake consumption (gō/week = 180 ml/week), VCM exposure concentration index, latent period (first exposure to 1979), cumulative exposure (years), ICG test, serum bilirubin, GOT, GPT, Al-P, GGT, ZTT, LDH, total cholesterol, TTT, A/G and thrombocytes.

The obesity index used by us, was weight/{height − (height + 151)/3}, where the denominator is the formula for determining the standard weight of Japanese according to Matsuki et al [1970]. The workers were divided into four groups by VCM exposure concentration. The VCM exposure concentration index was as follows: index 4 included workers involved in cleaning autoclaves and dehydration of polymerized vinyl chloride polymer (VCP); index 3 included workers involved in polymerization; index 2 included workers involved in drying of polymerized VCP; and in laboratory work related to polymerization; and index 1 included workers involved in tasks other than the above, such as production and analysis of VCM. Higher exposure concentration index indicated greater VCM exposure. More detailed information on VCM concentration in the working environments was not available.

Blood samples were analyzed by the same technician for four months; all analyses for each test (for example, GPT) were done using the same method. Liver function data of healthy subjects, also analyzed by the one technician, were within normal values; correlation coefficients between analyzed items did not differ greatly from values given in other reports [Wakabayashi et al, 1976].

RESULTS AND DISCUSSION

Table I presents means, standard deviations, numbers of samples, maximums, and minimums of the health examination indicators. The age distribution was skewed: range, 23–57 years with a mean of 48.0 years. The means of height, weight, and the obesity index are 164.2 cm, 59.8 kg, and 101.5% respectively. Sake consumption showed a range of 0–17.5 gō/week, with a mean and a standard deviation of 7.77 and 5.36 gō/week, respectively. The mean VCM exposure concentration index was 2.6.

TABLE I. Mean, Standard Deviation (SD) Number of Samples, Maximum and Minimum

	Mean	SD	No. of samples	Maximum	Minimum
1. Age (years)	48.0	6.6	108	57	23
2. Height (cm)	164.2	6.4	108	177	146
3. Weight (kg)	59.8	8.3	108	80	38
4. Obesity index (%)	101.5	11.1	108	136	78
5. Sake consumption (gō/week)[a]	7.77	5.36	108	17.5	0
6. Exposure concentration index	2.6	1.1	108	4	1
7. Latent period (years)	20.5	8.5	108	30.3	1.9
8. Cumulative exposure duration (years)	9.75	7.26	108	27.3	1.0
9. ICG (%)	9.9	3.9	95	24	1
10. Bilirubin (mg 100 ml)	0.88	0.28	108	1.6	0.4
11. GOT (units)	27.3	21.1	108	191	14
12. GPT (units)	20.9	17.8	108	150	7
13. Al-P (units)	7.4	2.3	108	20	4
14. GGT (units)	56.2	73.3	108	565	7
15. ZTT (units)	7.26	1.92	108	19.1	4.1
16. LDH (units)	191.	42.	108	304	72
17. Cholesterol (mg 100 ml)	192.	33.	108	310	123
18. TTT (units)	1.9	0.9	108	8.0	0.7
19. A/G	2.0	0.3	108	3.0	1.3
20. Thrombocytes (10^4 mm^3)	26.4	5.9	104	42.9	14.9

[a] 1 gō = 180 ml.

with 22, 27, 29, and 30 workers distributed among indices 1–4, a nearly uniform distribution.

The latent period and the duration of cumulative exposure ranged from 1.9-30.3 years and 1.0-27.3 years, respectively. The means of the blood chemistry results did not vary significantly from normal values. Some extraordinary values, ie, GOT 191 units and GPT 150 units for subject A, Al-P 20 units and GGT 565 units for subject B, and ZTT 19.1 units and TTT 8 units for subject C, were found. These values exceeded the mean plus four standard deviations; subjects A, B, and C are regarded as having had disordered liver functions. These six results cannot be derived from the normal distributions of liver function data of healthy subjects and were therefore excluded from the analyses. However, it should be mentioned that the statistical results obtained without using the six findings do not differ greatly from the statistical results obtained using the six.

Correlation coefficients between 20 examination items were calculated by number of workers, age groups (20–39, 40–49, or 50–59 years), VCM exposure concentration index (4, 3, 2, or 1) and cumulative exposure duration (0–4, 5–14, or 15–30 years). The distribution by age groups was 11, 43, and 54 workers for 20–39, 40–49, and 50–59 years, respectively. Distribution by cumulative exposure period was 37, 48, and 23 workers for 0–4, 5–14, and 15–30 years, respectively. Correlation coefficients between VCM exposure concentration index, latent period, or cumulative exposure duration and other examination items (for example GPT) were calculated by age group, exposure concentration index, and cumulative exposure duration: Table II shows statistically significant correlations. No consistently significant examination findings were observed. Examination results that were calculated by stratum and were

TABLE II. Significant Correlation Coefficient*

Stratum		Exposure concentration index	Latent period	Cumulative exposure duration
Total sample			Age ++, GOT +, GPT +, LDH +, A/G −−	Age +, LDH +
Age	20–39	A/G −	Age +, Al-P −	Age +, Al-P −
	40–49	ICG −, BIL +	Age ++, A/G −	BIL +
	50–59		GPT +, LDH +	LDH ++
Exposure concentration index	High (4)			
	Medium (3)		Age ++, Chol +	Age +
	Slight (2)		Age ++, A/G −	Al-P +
	Low (1)		Age ++, ZTT +, TTT +, THR −	GOT +, LDH ++
Cumulative exposure duration (years)	0–4	BIL ++	Age +	
	5–14	ICG −	Age ++, GPT +, A/G −−	
	15–30	GGT −	Al-P +	

*++, +, positive correlation, −−, −, negative correlation; +, − $p < 0.05$; ++, −−, $p < 0.01$
Chol, cholesterol; THR, thrombocytes.

significant twice are are ICG (negative correlation) and bilirubin (positive correlation). Negative correlation of the ICG indicated that an increase in VCM exposure reduced the value of ICG.

Consequently, the workers of this study can be regarded as having had no disorder of pigment excretion from the liver, owing to VCM exposure. This is not consistent with other reports [Kramer and Mutchler, 1972; Veltman et al, 1975] that investigated pigment excretion from liver using, for example, the BSP (bromosulfalein) test. No reports that showed a noteworthy relationship betwen bilirubin and VCM exposure were found. Our study only found a significant relationship between bilirubin and VCM exposure in two groups. Significant positive correlations were detected between age and latent period or cumulative exposure duration. Examination results that had more than one significant correlation were GOT(+), GPT(+), LDH(+), and A/G(−), each sign indicating the direction of the correlation coefficient. However, no significant examination result was found in the group with the highest VCM exposure concentration index.Accordingly, the detection of several significant correlations between examination results and the latent period or cumulative exposure duration may not be reliable. It should be mentioned that GOT, GPT, LDH, and A/G values were not within normal values in some elderly workers. Correlation analysis revealed, however, that no worker in this study consistently had marked liver dysfunction.

The correlation coefficients between the 12 examination items did not differ from those of another report [Wakabayashi et al, 1976], which studied laboratory data of healthy subjects. Age, the VCM exposure concentration index, and cumulative exposure duration were selected as three factors for analysis of variance (ANOVA), and two-way layout ANOVA [Scheffé, 1959]. These were calculated three (${}_3C_2 = 3$) times, assigning two factors to two of the three factors and a dependent variable to each examination item. The results of the ANOVA are not shown because few notable relations were found. However, there was a tendency for some examination items to have relatively high F values in the ANOVA for the age factor. This suggests that

some elderly workers had liver dysfunction consistent with the findings described above.

Stepwise regression analysis was performed with each of the 12 laboratory examination items. For each analysis, a dependent variable was assigned to a laboratory examination item and independent variables were assigned to all other items except age and the dependent variable. Table III shows accepted independent variables by dependent variable. The VCM exposure concentration index is associated with a negative coefficient when the dependent variable is ICG. This is equivalent to saying that the correlation coefficient between the ICG and the VCM exposure concentration index is negative and statistically significant. The results of the stepwise regression analysis do not differ greatly from those of other reports [Wakabayashi et al, 1976; Kitamura, 1980], in which laboratory examination data of healthy subjects was studied.

Since unusual findings among the workers were not detected by ANOVA or stepwise regression analysis, principal component analysis was carried out [Shioya and Asano, 1967; Okuno et al, 1971] to investigate latent relationships. According to this analysis, three factors with eigen values 2.0 or greater were selected from among the 20 examination items by principal component analysis. The summation of the communalities for the three factors was 0.383. Some values of the factor loadings for laboratory examination items were high, whereas the values for the VCM exposure indices were not elevated. This suggests that VCM exposure indices are in some category other than the laboratory examination items, and that results of the health examinations of the workers were not consistently related the VCM exposure concentration index.

The last analysis conducted was the canonical correlation coefficient [Okuno et al, 1978]. The first variable group of the analysis consisted of 12 laboratory examination results, ie, liver function tests and thrombocytes, and the second variable group consisted of 8 nonlaboratory examinations, ie, age, height, weight, obesity index, sake consumption, VCM exposure concentration index, latent period, and cumulative exposure duration. In this analysis, it was found that the sum of not only the VCM

TABLE III. Selected Independent Variables by Stepwise Regression Analysis*

Dependent variable	Independent variables
ICG	Exposure concentration − −, ZTT + +, Chol + +
BIL	Chol + +, A/G + +
GOT	Weight − −, GPT + +, GGT + +, LDH + +
GPT	Weight + +, GOT + +, LDH −
Al-P	Chol −
GGT	Sake +, GOT + +, Al-P +
ZTT	Chol −, TTT + +, A/G − −
LDH	GOT + +, GPT −
Chol	Obesity +, ICG +, BIL + +
TTT	GGT +, ZTT + +, Chol + +
A/G	Sake +, latent period − −, BIL + +, ZTT − −
THR	ICG − −, BIL + +, GGT +

*Chol, cholesterol; THR, thrombocytes; + +, +, positive regression coefficient; − −, −, negative regression coefficient; + +, − −, partial F value ≧ 7; +, −, 7 > partial F value ≧ 4.

exposure concentration index but also latent period, height, and sake consumption were related to A/G. This does not demonstrate that the VCM exposure concentration index necessarily affects the liver function of VCM workers. This resembles the stepwise regression analysis in which the dependent variable is A/G.

Additional findings about sake consumption are as follows: (1) sake consumption is not significant on ANOVA where the factor is age, VCM concentration index, or cumulative duration; and (2) the correlation coefficient between sake consumption and GGT or A/G is statistically significant.

CONCLUSIONS

Relationships between a VCM exposure concentration index and (1) reduction of pigment excretion from liver, such as ICG; (2) decrease of thrombocytes; or (3) elevation of Al-P, GGT, and other enzymes were not detected among workers exposed to VCM. No remarkable changes of bilirubin, transaminases, flocculation reaction tests or others were found. Thus, no specific disorder of liver function was detected among the VCM workers in this study. At the present time, it is not known whether or not these VCM workers will suffer from hepatoangiosarcoma at a later time. Certainly, early abnormalities were not detected, with the diagnostic tests used.

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