medichem

OCCUPATIONAL HEALTH IN THE CHEMICAL INDUSTRY

Papers presented at the
XVII Medichem Congress
Cracow, Poland
26–29 September 1989

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR EUROPE
COPENHAGEN

X-1711-(100)

BIOLOGICAL AND HEALTH MONITORING OF WORKERS EXPOSED TO VINYL CHLORIDE

T. Popov, B. Galunska, and S. Tsankova

Institute of Hygiene and Occupational Health,
Medical Academy Sofia, Bulgaria

INTRODUCTION

During long-term low-level occupational exposure, a gradual transition from health to illness may take place. The progression from health to disease goes through the following stages: absence of effect - compensated effect - early health disturbances - manifest disease. The experience of periodic check-up examinations shows that pathology related to toxic chemicals is easily diagnosed, especially when a target-oriented search is undertaken for characteristic clinical signs. These examinations are thus aimed at finding disease at an early clinical stage.

Much more effective, though far more difficult, is the detection of health impairment. One major constraint on detecting early adverse health effects in an occupationally exposed population is the difficulty of distinguishing a physiologically normal condition from a compensatory pathology. This is attained by a systematic surveillance of the different biochemical parameters related to the mechanisms of the toxic effect.

The choice of adequate tests for biological monitoring in occupational medicine will depend on the knowledge available and the mechanisms underlying the development of an adverse health effect. An adequate diagnostic test may be based on parameters manifesting the primary toxic effect, on the structural changes in the critical organ, or on the functional straining of adjustment mechanisms induced by the primary toxic effect. Up to the late 1960s, vinyl chloride monomer (VCM) and polyvinyl chloride were thought to be entirely inert. During the 1970s, the situation was dramatically altered by reports of different hepatic abnormalities among vinyl chloride workers and the discovery of some cases of angiosarcoma of the liver. Later, the toxic effects of VCM were found to depend on its biotransformation to more toxic metabolites in the liver via the monooxygenase enzyme system, known also as mixed-function oxidases (MFO). A direct relation between activity of MFO and toxicity of VCM has been confirmed in experimental animals by a number of authors [1-3].

A literature search failed to find any data on the use of MFO activity changes for the purposes of biological monitoring.

MATERIALS AND METHODS

At the end of 1988, 137 workers exposed to VCM in a polyvinyl chloride production plant were investigated. Of these, 127 showed abnormal findings during the screening of more than 500 workers from the same plant in 1987. In addition, 10 newly employed operators and fitters exposed to higher VCM concentrations were tested.

MFO activity was determined by the method developed by Popov et al. [2]. This method consists of peroral loading with 6 mg/kg aminopyrine (AP) and colorimetric determination of its main metabolites 4-aminoantipyrine (4AAP) and N-acetyleaminoantipyrine (N-AcAAP) in 6-hour urine samples. In the first stage, AP undergoes N-demethylation with participation of MFO. The obtained 4AAP undergoes acetylation to form the conjugate N-AcAAP.

A target-oriented search was undertaken by a gastroenterologist and neurologist for early clinical signs of chronic VCM intoxication.

RESULTS

Heptomegaly is most frequently combined with deviations in the activity of SGOT, SGPT, GGTP, induction or inhibition of MFO, increased G-6-PD activity, and increased lipid peroxide content (Table 1). The signs suggesting Raynaud-like phenomenon most frequently are combined with MFO inhibition and decrease of reduced glutathione.

Table 2 shows the correlation of indices. There is 100% correlation between MFO inhibition and the decrease of the reduced glutathione. The most frequently found correlation is between MFO changes and deviations in the other indices. With regard to diagnostic significance, they are followed by the changes in GGTP, SGOT and lipid peroxides.

The subjects varied in the intensity and duration of their exposure to VCM. For this purpose we used the formula proposed by Kassurov for determining the index of exposure: $IE = C \times T$, where IE is the index of exposure, C, the average shift concentration of the toxic agent on the workplace (in mg/m^3), and

Table 1. *Correlation of biochemical parameters with clinical symptoms of chronic intoxication with VCM.*

Parameter	No. of subjects	n_c	Deviation (%)	Hepatomegaly n	n_c	%	Vasomotor disturbances[1] n	n_c	%
SGOT	137	100	73	100	39	39	100	38	38
SGPT	137	109	80	109	43	39	109	43	39
AP	137	65	47	65	19	29	65	20	21
GGTP	137	24	18	24	11	46	24	9	38
4AAP	93	37	40	37	13	35	37	12	32
N-ACAAP	92	38	41	38	16	42	38	12	32
4-AAP	93	9	10	9	1	11	9	7	78
N-AcAAP	92	4	4	4	2	50	4	4	100
G-6-PD	118	35	30	35	13	37	35	13	37
Vitamin E	130	67	52	67	25	37	67	26	39
Reduced glutathione	130	69	54	69	27	39	69	32	46
Haemolytic resistance	124	26	21	26	9	35	26	9	35
Lipid peroxide	131	56	43	56	29	39	56	25	45

SGOT = Serum glutamic opalacetic transaminase. SGPT = Serum glutamic pyruvic transaminase. AP = Aminopyrine. GGTP = Gamma-glutamyl transpeptase. 4AAP = 4-Aminoantipyrine. N-AcAAP = N-Acetyleamionantipyrine. G-6-PD = Glucose-6-phosphate dehydrogenase. n_c = Number of subjects with abnormal findings.

[1] Reynaud-like phenomenon.

Table 2. *Correlation in the deviations from referent values of the biochemical parameters (in %).*

Parameter	SGOT	SGPT	AP	GGTP	4AAP	N-Ac-AAP	4AAP	N-Ac-APP	G-6-PD	Vitamin E/	Reduced glutathione	Haemolytic resistance	Lipid peroxide
SGOT	x	76	58	11	63	58	0	5	33	46	39	26	44
SGPT		x	56	12	26	48	13	0	28	40	45	21	46
AP			x	13	59	41	12	0	26	39	38	22	43
GGTP				x	40	0	0	0	50	14	86	14	71
4AAP					x	59	x	0	38	53	21	29	56
N-Ac-AAP						x	0	x	23	43	30	15	69
4AAP							x	20	0	20	100	0	60
N-Ac-AAP								x	0	0	0	0	0
G-6-PD									x	53	31	27	47
Vitamin E										x	32	17	50
Reduced glutathione											x	13	54
Haemolytic resistance												x	64
Lipid peroxide													x

SGOT = Serum glutamic opalacetic transaminase. SGPT = Serum glutamic pyruvic transaminase. AP = Aminopyrine. GGTP = Gammaglutamyl transpeptase. 4AAP = 4-Aminoantipyrine. N-AcAAP = N-Acetyleamionantipyrine. G-6-PD = Glucose-6-phosphate dehydrogenase.

T is average time (in minutes) spent at the same workplace. In the cases where the worker had several workplaces with different VCM concentrations, a summed up index of exposure was calculated.

Table 3 shows the exposure-response of workers. Laboratory assistants have the lowest exposure followed by electricians, operators, and fitters. The frequency of clinical symptoms of chronic vinyl chloride intoxication increases with length of service. The deviations in the biochemical indices appear significantly before clinical symptomatology. The earlier the deviations are found, the more significant the exposure.

The correlation between intensity and duration of exposure on the one hand and the deviations on the other hand is best observed in the group of operators. With the length of service only, the number of the cases with biochemical deviations decreases, while the number of cases with clinical symptoms increases.

DISCUSSION

The data offer a reasonable support to our hypothesis that the pathogenesis of vinyl chloride intoxication includes a "triggering mechanism" of the toxic effect as well as its development, leading to characteristic clinical manifestations. The high frequency of MFO induction combined with hepatomegaly would indicate that the triggering mechanism of the intoxication is related to biotransformation of vinyl chloride into chlorethylene oxide, an exposidation that occurs with the participation of MFO. This explains the MFO induction as an adaptation to intake of high quantities of xenobiotic vinyl chloride. The MFO induction in turn, presupposes the activation of G-6-PD as a generator of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a donor of electrons for reduction of cytochrome P-450 and its inclusion in the cycle for metabolizing the vinyl chloride. Chlorethylene oxide is highly toxic at the site of its formation in the endoplasmatic reticulum of the hepatocyte. The structural damage of lipoproteinic biomembranes is related to abundant formation of lipid peroxides. This also explains the tendency towards exhaustion of tocopherol as a powerful antioxidant, which renders harmless the generated lipid peroxides.

Further, the generated chlorethylene oxide conjugates with the reduced glutathione, which explains the exhaustion of the glutathione. The reduced level of glutathione interferes with the function of the glutathione redox system, which is respon-

Table 3 *Exposure-response in workers exposed to VCM.*

Years of exposure		Laboratory assistants <1	1–3	3–5	5–10	>10	Electricians <1	1–3	3–5	5–10	>10	Operators <1	1–3	3–5	5–10	>10	Fitters <1	1–3	3–5	5–10	>10
With clinical signs	N	0	0	0	6	2	0	1	0	1	12	8	10	9	22	30	2	0	3	6	23
	n_c	0	0	0	1	1	0	0	0	0	9	0	4	4	13	23	1	0	2	2	13
	%	0	0	0	17	50	0	0	0	0	75	0	40	44	59	77	50	0	67	33	57
With biochemical deviations	N	0	0	0	6	2	0	1	0	1	12	8	10	9	22	30	2	0	3	6	23
	n_c	0	0	0	5	1	0	1	0	1	3	8	6	5	9	12	1	0	1	4	10
		0	0	0	83	50	0	100	0	100	25	100	60	56	41	23	50	0	33	67	44

N = Number of subjects tested. n_c = Number of subjects with abnormal results.

sible for rendering harmless the lipid peroxides. On the other hand, the increased amount of products of lipid peroxidation in blood interferes with the haemolytic resistance of the erythrocytes.

The increase of transaminases and GGTP is explained by the toxic effect of epoxide upon biomembranes and on the cytomembranes of hepatocytes in particular. This determines the disturbance of the permeability and transfer of these enzymes from hepatocyte to blood.

CONCLUSIONS

The adaptation of the organism to the effect of vinyl chloride is manifested by MFO induction. The functional capacity of a given organ may be increased through structural changes, expressed in hyperplasia and regeneration (i.e. increase in the size and number of hepatocytes). A clinical manifestation of this process is hepatomegaly, a straining of the compensatory mechanisms. Of a special interest is the increase in the number of cases of MFO inhibition in workers with prolonged exposure to high concentrations of vinyl chloride. Without doubt, this effect is related to a breakdown of the mechanisms of adaptation. Clinically, it is combined with more frequent cases of neurovegetative syndrome and strengthening of its manifestations. Parallel with MFO inhibition, more cases are occurring with lower content of reduced glutathione (100 %) and higher level of lipid peroxides.

These data prove that chronic intoxication with VCM proceeds in two stages: pre-clinical and clinical. The first represents a pre-morbid state, when the absence of any clinical symptoms (including subjective complaints) is combined with changes in a number of biochemical indices. Continued exposure to high concentrations leads to clinical symptoms. The clinical manifestation also proceeds in two stages. In the first stage the clinical symptoms are combined with MFO induction. The second stage is characterized by the strengthening of the clinical symptoms, when the MFO induction is related by a diametrically opposed state: inhibition of the enzyme system and further exhaustion of the glutathione due to disturbances in its synthesis.

The results of the biological monitoring and targetoriented medical examination show that the frequency and severity of adverse health effects of workers are directly dependent on type of work and length of service.

REFERENCES

1. Jaeger R.J. et al. Acute hepatic injury by vinyl chloride in rats pretreated with phenobarbital. Nature, 252: 724-726 (1974).

2. Popov, T. and Leonenko, O. Method for assessing the activity of liver oxidases. Gigiena i sanitarya, 9: 56-59 (1977) (in Russian).

3. Wisniewska-Knypl, J.M. & Klimczak, J. Activity of liver microsomal monooxygenases in the course of chronic exposure of rats to vinyl chloride monomer. Paper presented at the 6th Medichem Conference, Dubrovnik, 1978, pp. 85-88.