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Influence of Genetic Polymorphism of Styrene-Metablizing Enzymes on Occupational Exposure Monitoring to Styrene

Wei Qu, Fang Zhang*

Shandong Academy of Occupational Heath and Occupational medicine, Jinan, China
Email: *zhangfang2816@sina.com

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Abstract

In this study, we selected 58 styrene-exposed workers, measured personal styrene exposure, evaluated genotypes relevant drug-metabolizing enzymes (CYP2E1, EPHX1, GSTM1 and GSTT1) which may explain the variability in the urinary metabolite excretion. The results showed that, in different levels of styrene exposure groups, there is a significant association between urinary metabolites and some genotypes of styrene-metabolizing enzymes, including CYP2E1 (5-flanking region, RsaI/PstI), GSTM1(gene deletions) and EPHX1(predicted activity).

Keywords

Styrene, Mandelic Acid (MA), Phenylglyoxylic Acid (PGA), Phenyl Hydroxyethyl Mercapturic Acids (PHEMA), Biological Monitoring, Genetic Polymorphisms

1. Subjects and Methods

1.1. Study Subjects

We collected 58 male workers as study subjects, they are 20 - 42 years old, employed in a fibre glass-reinforced plastic boat plant in China, a questionnaire was also taken to them.

1.2. Methods

The study was carried out in November, 2013. Prior to the study, a questionnaire was administered to all subjects concerning health status, smoking, alcohol consumption, medication and occupational history.

Environmental and biological monitoring was taken to evaluate the concentration of styrene exposure which including personal air sampling, urine samples and blood samples for DNA extraction.

Based on all above, determination-of-genotypes and statistical analyses was made.

*Corresponding author.

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2. Results

2.1. Allelic Frequencies in Study Population

The distribution of genotypes in each group was in Hardy-Weinberg equilibrium, except for GSTM1 and GSTT1 (**Table 1**). The predicted enzymatic activity level for EPHX1 was classified on the basis of codon 113 and 139 [1].

2.2. Relationship between Styrene Exposure and Urinary Metabolites

It was observed that there was a significant correlation between styrene concentration in air and MA, PGA and PHEMA (**Table 2**) ($P < 0.05$).

2.3. Analysis of Association between Genetic Polymorphisms of Biotransformation Enzymes and Urinary Metabolites (Shown in Table 3 and Table 4)

Through statistical analyses, we found that in low-exposure group, the CYP2E1 (5-Flanking RsaI/PstI) C1/C2 and C2/C2 individuals have significantly higher urinary levels of MA, PGA and PHEMA ($P < 0.05$). In high-exposure group, we can't find the effect. In both low and high exposure group, the GSTM1 null individuals have significantly lower urinary levels of PHEMA ($P < 0.05$). As for EPHX1, the levers of MA and PGA in subjects with low enzyme activity was significant lower than that in subjects with medium or high enzyme activity ($P < 0.05$) in both groups. There are no significant difference found between other genotypes and urinary metabolites.

Table 1. Allelic frequencies in study population.

Genotype	Number (%)
CYP2E1	
5_-Flanking RsaI/PstI	
c1/c1	37 (66.07)
c1/c2	18 (32.14)
c2/c2	1 (1.79)
CYP2E1	
intron 6 DraI	
D/D	39 (70.16)
C/D	17 (29.84)
EPHX1	
Exon 3	
Tyr/Tyr	15 (26.79)
Tyr/His	30 (53.57)
His/His	11 (19.64)
EPHX1	
Exon 4	
His/His	32 (57.14)
His/Arg	24 (42.86)
EPHX1	
Predicted activity*	
Low activity	27 (48.21)
Medium activity	19 (33.93)
High activity	10 (17.86)
GSTM1	
Positive	22 (39.29)
Null	34 (60.71)
GSTT1	
Positive	30 (53.57)
Null 34	26 (46.43)

*In DNA extraction,two samples failed; *Low activity: His/His-His/His, His/His-His/Arg, Tyr/His-His/His, His/His-Arg/Arg; medium activity: Tyr/Tyr-His/His, Tyr/His-His/Arg, Tyr/His-Arg/Arg; high activity: Tyr/Tyr-Arg/Arg, Tyr/Tyr-His/Arg.

Table 2. Correlation coefficients in general regression analysis between styrene exposure and urinary metabolites.

Variable	MA	PGA	PHEMA
Styrene exposure	0.861*	0.868*	0.937*

*$p < 0.01$.

Table 3. Influence of genetic polymorphisms on urinary metabolites in occupational exposure to styrene in low-exposure group.

Genotypes	n	MA (mg/g Cr), Mean (S.D.)	PGA (mg/g Cr) Mean (S.D.)	PHEMA (mg/g Cr), Mean (S.D.)
CYP2E1				
5_-Flanking				
c1/c1	17	72.55 (32.64)	57.16 (26.40)	6.40 (4.06)
c1/c2 and c2/c2	9	112.28 (33.43)	87.70 (26.70)	9.80 (1.07)
CYP2E1				
intron 6 DraI				
D/D	18	90.67 (40.40)	71.82 (32.82)	7.23 (5.10)
C/D	8	76.47 (30.28)	58.53 (22.52)	6.25 (3.53)
EPHX1				
Predicted activity*				
Low activity	13	68.90 (22.35)	57.72 (22.46)	7.83 (3.89)
Medium activity	9	92.57 (39.39)	68.52 (27.24)	8.32 (4.01)
High activity	4	128.74 (42.35)	98.48 (41.91)	8.98 (2.53)
GSTM1				
Positive	9	89.37 (36,78)	68.87 (33.78)	10.41 (4.56)
Null	17	82.49 (32.77)	71.23 (29.89)	5.08 (3.55)
GSTT1				
Positive	14	79.93 (28,97)	67.30 (30.93)	7.18 (4.58)
Null	12	87.69 (34.53)	72.79 (29.59)	6.63 (4.85)

Table 4. Influence of genetic polymorphisms on urinary metabolites in occupational exposure to styrene in high-exposure group.

Genotypes	n	MA (mg/g Cr), Mean (S.D.)	PGA (mg/g Cr) Mean (S.D.)	PHEMA (mg/g Cr), Mean (S.D.)
CYP2E1				
5_-Flanking				
c1/c1	20	266.99 (126.99)	219.60 (100.51)	31.05 (7.61)
c1/c2 and c2/c2	10	232.99 (93.34)	194.93 (73.84)	29.34 (7.89)
CYP2E1				
intron 6 DraI				
D/D	21	248.59 (111.41)	214.85 (95.01)	30.69 (7.04)
C/D	9	271.69 (132.81)	203.28 (89.22)	29.88 (9.25)
EPHX1				
Predicted activity*				
Low activity	14	170.41 (82.96)	146.58 (76.87)	29.96 (4.79)
Medium activity	10	304.29 (75.89)	250.54 (70.87)	31.25 (7.24)
High activity	6	372.80 (93.50)	297.29 (30.44)	32.11 (7.47)
GSTM1				
Positive	13	256.71 (76.53)	207.78 (98.02)	34.13 (5.11)
Null	17	247.28 (89.20)	221.23 (87.36)	27.63 (8.13)
GSTT1				
Positive	16	256.36 (102.34)	212.58 (103.27)	31.89 (8.11)
Null	14	261.92 (124.57)	218.93 (97.63)	28.80 (6.93)

3. Discussion

The three urinary metabolites (MA, PGA, PHEMA) can be regarded as biomarkers of occupational exposure to styrene, since a significant correlation was observed between 8h time-weighted average (TWA) and urinary metabolites levels.

The results obtained could be related with genotype of C1/C2 and C2/C2 have stronger transcription activity [2], and at high styrene concentrations, CYP2B6 seems to be the main metabolizing enzyme involved in the metabolism of this compound [3].

Our study showed that excretion of PHEMA in urine is significantly lower in GSTM1 null individuals. Perhaps, in detoxification of styrene, GSTM1 may perform an important role.

We also found EPHX1 polymorphisms is significant in styrene metabolism. It may be speculated EPHX1 may create some kind of basis for toleration of adverse effects of styrene exposure. Additionally, epoxide hydrolase rapidly converts genotoxic to phenylethylene glycol, which is considered as rather non-toxic. A lack of information exists on the possible adverse effect of phenylethylene glycol accumulation in the case of excessive styrene exposure.

On the other hand, there were a few limitations in this study. First, the possible influence of co-exposure to other chemicals in workshops on styrene metabolism was not considered. Second, our results are encouraging to continue such a kind of study in a larger population, employing more biomarkers and concentrating on metabolic aspects (e.g. concentration in blood) as well as on enzyme phenotypes.

4. Conclusion

In conclusion, this study shows that the genetic polymorphisms of drug-metabolizing enzymes may have some influence on the main metabolites of styrene. Although urinary styrene metabolites are good biomarkers of internal styrene dose in occupational exposure, our study suggests that genetic susceptibility of the individual should also be considered in biological monitoring of exposure to styrene.

Research Projects

2013 science and technology development plan of Shandong Province Science and Technology Agency (2013YD18027); 2013 Technology Project of Major accident prevention Key technologies for Safe Production (LAJK2013-112).

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