Environmental Toxicology and Pharmacology 53 (2017) 89–94

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Research Paper

The relationships between arsenic methylation and both skin lesions and hypertension caused by chronic exposure to arsenic in drinking water

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ARTICLE INFO

Keywords:
Arsenic
Methylation
Skin lesions
Hypertension
Drinking water

ABSTRACT

The associations between arsenic exposure, arsenic methylation, and the prevalence of skin lesions and hypertension are investigated. The results indicate that the HS (hypertension and skin lesions) group and the S (skin lesions) group have higher urinary concentrations of iAs (inorganic arsenic), MMA (monomethylarsonic acid), DMA (dimethylarsinous acid) and%MMA, and lower SMI (secondary arsenic methylation index) compared to the H (hypertension) and N (without both hypertension and skin lesions) groups. The arsenic content in water which caused H may be lower than that which caused HS and S. In addition, the odds ratios suggest that higher urinary concentrations of iAs and MMA, %iAs, %MMA and PMI elevate the prevalence of only hypertension and skin lesions, and both hypertension and skin lesions. However, higher%DMA and SMI, and lower%MMA increase the prevalence of both hypertension and skin lesions compared to that of only skin lesions. It can be concluded that skin lesions subjects have higher prevalence of hypertension. Hypertension subjects may have higher prevalence of skin lesions. Lower%DMA and SMI, higher%iAs, %MMA and PMI enhance the prevalence of only hypertension and skin lesions, and both hypertension and skin lesions. Moreover, iAs and MMA may have higher toxicity and lead to both hypertension and skin lesions than to only hypertension.

1. Introduction

Arsenic is highly toxic to humans (Kapaj et al., 2006; Abdul et al., 2015). Groundwater arsenic contamination is a serious public health concern worldwide (WHO, 2011). Evidence from previous studies suggests that the oxidation state of arsenic and its degree of methylation affect the toxicity of arsenicals. The iAs (inorganic arsenic, include trivalent As^{III} and pentavalent As^{V}), particularly As^{III} has the highest toxicity and MMA (monomethylarsonic acid) is more toxic than DMA (dimethylarsinous acid) (Petrick et al., 2001; Hirano et al., 2003). Arsenic is considered a Category I human carcinogen by the International Agency for Research on Cancer (IARC) (US EPA, 2006, 2015). The maximum permissible concentration of iAs in drinking water, as recommended by the World Health Organization (WHO) and the US Environmental Protection Agency, is 10 μg/L (US EPA, 2006, 2015).

Subjects chronically exposed to high concentrations of arsenic in drinking water can develop skin lesions, including hyperkeratosis, depigmentation and pigmentation (Karagas et al., 2015; Yang et al., 2002). Many studies have reported that the specific profile patterns of arsenic metabolites in urine are associated with skin lesions and other arsenic-related health effects. In general, higher levels of%iAs and% MMA, and lower levels of%DMA in urine elevate the risk of skin lesions (Kile et al., 2011; Naranmandura et al., 2007; Wen et al., 2012; Zhang et al., 2014). Similarly, a higher primary arsenic methylation index (PMI, proportion of methylate iAs to MMA) and lower secondary arsenic methylation index (SMI, proportion of further methylate MMA to DMA) can increase the risks of skin lesions (Wei et al., 2016; Yang et al., 2017).

Recently, it was reported that exposure to iAs increased the risk of elevated blood pressure (Abhyankar et al., 2012; Chen et al., 2011; Medrano et al., 2010). Arsenic exposure was associated with an increase in blood pressure in pregnant women (Farzan et al., 2015). Some researches reflected that the risk of hypertension is influenced by arsenic exposure, arsenic methylation index and the profiles of arsenic metabolites in urine (Zhang et al., 2013; Jiang et al., 2015). Higher MMA concentrations in urine and a lower secondary methylation index (SMI) may increase susceptibility to hypertension. In addition, lower% DMA may be correlated with an increased risk of hypertension (Li et al.,

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http://dx.doi.org/10.1016/j.etap.2017.05.009
Received 9 March 2017; Received in revised form 9 May 2017; Accepted 10 May 2017
Available online 12 May 2017

2013; Huang et al., 2007). Li et al. (2015) suggested that inefficient arsenic methylation capacity may increase hypertension risk.

However, little is known about the relationships between arsenic methylation and both skin lesions and hypertension caused by exposure to iAs in drinking water. Therefore, the subjects included in the present study were divided into four groups based on the diagnosis of skin lesions and hypertension. Subjects with both skin lesions and hypertension were included in the HS group, subjects only with skin lesions were included in the S group and subjects only with hypertension were included in the H group. Subjects without skin lesions and hypertension were included in the N group. The main objectives of this study were to determine the prevalence of hypertension in the S group and the prevalence of skin lesions in the H group. The arsenic metabolites (iAs, MMA and DMA) in urine were determined and the main risk factors for HS, S and H were estimated by logistic regression analysis.

2. Materials and methods

2.1. Study area and subjects

The study area, Bameng region, is located north of the Yellow River in western Inner Mongolia, P.R. China. In this area, the groundwater contains high concentrations of arsenic. The residents in this area suffer from arsenic-related health effects caused by exposure to arsenic contaminated drinking water (Deng et al., 2009; Guo et al., 2011). Subjects who had ingested seafood in the past week, taken blood pressure medication, and pregnant women were excluded. A total of 479 adults in the area, including 134 males and 345 females, were selected for investigation. The average age of the female and male were 41.9 (range:18–66) and 41.2 (range:18–62) years, respectively. 139 study subjects were smokers and 63 study subjects were alcohol consumer.

At the beginning of the survey, all participants read and signed the informed consent. The procedures performed in this study were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. A questionnaire which included information on gender, age, living conditions, dietary habit, smoking, alcohol consumption, and illness was completed by all participants. The subjects were divided into the HS, S, H and N groups.

2.2. Sample collection

Approximately 50 mL of voided first-morning urine was obtained in 50 mL polypropylene tubes from each subject. These urine samples were immediately stored in an icebox. All the urine samples were transferred to the Inner Mongolia Center for Endemic Disease Control and Research in Hohhot within 8 h and stored at −20 °C in a low temperature refrigerator. The urine samples were then placed in an icebox and transported to the Laboratory of Arsenic Analysis in the Institute of Geographic Sciences and Natural Resources Research, CAS (Beijing, China), and stored in a low-temperature refrigerator until analysis. With regard to water sampling, in order to remove water at the tip of the tap, the Tube well water was pumped for approximately 5–10 min before the water sample was collected. Approximately 50 mL of groundwater from the family wells used for drinking was then collected from each of the studied households. The water samples were stored in clean 50 mL bottles, and stored at −20 °C in a low temperature refrigerator along with the urine samples.

2.3. Determination of urinary arsenic speciation

Inorganic arsenic (including iAs^{III} and iAs^{V}), MMA and DMA in the urine samples were separated using a high-performance liquid chromatography/hydride generator (HPLC) (Gamble et al., 2005). The concentrations of iAs, MMA and DMA in the urine samples were determined by inductively coupled plasma-mass spectrometry (ICP-MS). Total arsenic contents in the drinking water were also determined by HPLC and ICP-MS. The analysis of standard reference materials from the National Center for Standard Reference Materials (1000 mg/L) was performed for quality control of arsenic determination. The recovery of iAs, MMA and DMA was 96%, 105% and 94%, respectively. Duplicate measurements of randomly selected urine samples were conducted. The mean deviation was less than 6%.

2.4. Blood pressure (BP) measurement and diagnosis of skin lesions

BP was measured according to the standard protocol recommended by the World Health Organization (Rose et al., 1982). Individuals participating in this study were not using prescription or traditional drugs to treat hypertension. The BP of each participant was measured three times in one day by trained clinicians using a mercury sphygmomanometer in the sitting position after resting for at least 15 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined at the first and fifth Korotkoff sounds, respectively. Subjects with a SBP ≥ 140 mmHg or DBP ≥ 90 mmHg were diagnosed as having hypertension.

In addition, skin lesions were diagnosed by two trained and experienced clinicians qualified in arsenism from the Inner Mongolia Center for Endemic Disease Control and Research. The diagnostic criteria used were according to the national standard (Standard of Diagnosis for Endemic Arsenism, WS/T-211-2001). Hyperkeratosis, depigmentation and chromatosis were considered as skin lesions.

2.5. Statistical analysis

Total arsenic concentration in urine (TAs) was defined as the sum of iAs and its metabolites. This was calculated as iAs + MMA + DMA. The arsenic methylation indices were defined as the percentages of the respective arsenic species in urine. Therefore, the primary methylation index (PMI) was calculated as the ratio between MMA + DMA and TAs, and the secondary methylation index (SMI) was calculated as the ratio between DMA and MMA + DMA (Sun et al., 2007).

Logistic regression models were then used to estimate the multivariate-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for the risk of skin lesions, hypertension or both skin lesions and hypertension. The S, H and N groups were used as the reference groups. The models were constructed using the various arsenic metrics individually tested with adjustment for smoking, drinking, age, sex, and BMI. The differences of arsenic among the groups were estimated by ANOVA (analysis of variance).

All statistical analyses were performed using the SPSS 18.0 software package for Windows.

3. Results

3.1. Prevalence of hypertension and skin lesions

The prevalence of hypertension in subjects with and without skin lesions is listed in Table 1. 69 subjects with skin lesions also had hypertension. The prevalence of hypertension in female subjects with skin lesions was 38.74% and was 49.06% in male subjects with skin

Table 1
Prevalence of hypertension (%) in subjects with and without skin lesions.

Item	Skin lesions group			Without skin lesions group			RR
	Cases	Total	%	Cases	Total	%	
Female	43	111	38.74	79	234	33.76	1.15
Male	26	53	49.06	27	81	33.33	1.47
Total	69	164	42.07	106	315	33.65	1.25