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Case Report

Electrocardiographic Changes in Occupational Exposure to Arsenic

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Abstract:

Arsenic (As) and its poisonous effects, toxic nature and carcinogenic effects are well-documented. As an environmental toxicant, As widely appears in nature in both its organic and inorganic form. As an occupational toxicant, As is shown to be linked to an increased risk in many cardiovascular diseases including hypertension, ischemic heart disease, peripheral arterial disease (also known as Blackfoot disease), and carotid atherosclerosis. QT prolongation is a frequently seen effect of as poisoning and a dispersion of QT is implicated in the genesis of ventricular arrhythmias as well as a direct predictor of cardiovascular mortality. A total of 207 metal-mine workers, who were admitted to the Ankara Occupational Diseases Hospital for a routine annual follow up, were enrolled in the study. A control group was composed of 207 healthy individuals who were screened for arrhythmias, hypertension and obstructive coronary artery disease. Patients being treated with a medication that could affect the QT interval and patients with the conditions, were excluded from the study. Statistical differences were analysed by performing independent sample t-tests. Our study showed a significant difference in the QT max between healthy individuals and the subjects with high occupational As exposure (P=0.039). QT dispersion and an As level in the hair samples, also showed a significant difference between the study groups (p=0.002 and p=0.001 respectively). Possible occupational exposure to As may cause cardiac arrhythmias and sudden cardiac death. Further studies are needed to document the increased cardiac risk in populations with environmental and occupational exposure.

1. Introduction

Arsenic (As), known as the king of the poisons and the poisons of the king, is believed to have been initially obtained by Albert Magnus in 1250 A.D. Since that time, its poisonous effects, toxic nature and cancerogenic effects are well-documented. As an environmental toxicant, As widely appears in nature in both its organic and inorganic form. Exposure to arsenic occurs in many ways, but mostly by arsenic polluted drinking water, occupational, and by medicinal sources as in pro-myelocytic leukaemia therapy. The maximum level of arsenic in drinking water must be under the level of 10 µg/L as set by the US environmental protection agency [1, 2]. Chronic exposure to As via drinking water or by inhalation as an

occupational toxicant, is shown to be linked to an increased risk in many cardiovascular diseases, including hypertension, ischemic heart disease, peripheral arterial disease (also known as Blackfoot disease), and carotid atherosclerosis [3-5] in a dose-response relationship [6]. Non-cardiac diseases such as hypo and hyperpigmentation of the skin, bladder cancer and lung cancer in heavy smokers, can be seen in people with high levels of exposure [7-9]. As a carcinogenic agent, As is classified as a group 1 and a group A by the international agency for research for cancer and the U.S. EPA [10, 11]. Carotid artery disease, coronary atherosclerosis and peripheral arterial disease may be caused by the direct cardiovascular toxic effects of the arsenic induced by its oxidative injury to the endothelial cells, proliferative effect on smooth muscle cells, macrophages and endothelial cells [12], or by an indirect mechanism that may have an underlying effect on the cardiovascular risk factors such as, hypertension, diabetes and hypercholesterolemia.

Various effects of toxic arsenic levels on a surface ECG have been observed in cases of occupational exposure and through the therapy for acute pro-myelocytic leukaemia with arsenic. QT prolongation is a frequently seen effect of arsenic poisoning and dispersion of QT is implicated in the genesis of ventricular arrhythmias and as a direct predictor of cardiovascular mortality [2, 13, 14]. A QT interval on the surface ECG is determined by the width of the ventricular action potential throughout the whole myocardium and is a presentation of repolarization time in the ventricles [15]. In the general population, the duration of the QT interval varies between 430 to 480 msec and can show differences according to age, gender, heart rate, medications, and the underlying heart disease [16]. The effect of Arsenic on the potassium channel is well studied [17-19] as ventricular repolarization is mostly dependent on potassium efflux. Arsenic prolongs the QT interval by potassium currents IKr and IKs [20, 21]. In this study, our aim was to determine the effect of arsenic on the QT interval and the QT dispersion in workers exposed to high levels of occupational arsenic.

2. Materials and methods

2.1. Patients and Methods

Occupational arsenic exposure could take place in industrial areas such as the glass industry, wood preservation, semiconductor production lines, in agricultural workers where arsenic is used as a desiccant and defoliant, and in the production of semi ferrous metals like gold and copper. A total of 207 metal-mine workers, who were admitted to the Ankara Occupational Diseases Hospital for a routine annual follow-up, were enrolled in the study. A control group was composed of 207 healthy individuals who were screened for arrhythmias, hypertension and obstructive coronary artery disease. Patients were treated with a medication that could affect the QT interval and those patients with the conditions were excluded from the study. A blood sample of every participant was collected for biochemical analysis and a complete blood count and a surface 12-lead ECG was obtained. All participants provided a written informed consent at the time of the enrolment. The study was approved by the Ankara Occupational Diseases Hospital ethics committee. The control group was formed from age, sex and risk factor matched volunteers. Weekly work hours of each participant, the type of industry they were working in, the duration of arsenic exposure, medical history and arsenic levels from their previous medical follow-ups were collected.

2.2. Hair Sampling

As a part of the annual follow-up, hair samples were taken from each worker, stored in a cooling bag without any chemical addition and transported to the centre for analysis. Arsenic levels were analysed in the Ankara Hifzissiha laboratories. Hair samples were washed with 0.1 % triton-X solution and dried at room temperature for 24 hours. Specimens of 0.1 gr were weighed and transferred to Teflon tubes. 5 mL of concentrated nitric acid solution was added into the tubes. Digestion procedure for hair samples was carried out using a CEM Mars Xpress microwave system (1600W oven at 200 °C for 15 minutes). Every sample was transferred from the microwave test tubes to polypropylene flasks and filled with distilled water up to 10 ml. In this study, Varian AA 240 Z Graphite Atomic Absorption Spectrometry (GFAAS) equipped with Zeeman background correction system was utilized for as determination. All the samples were kept at +4 °C in a refrigerator. Ultra-pure nitric acid and deionized water were used throughout all the analyses. All chemicals used were of analytical reagent grade. A standard solution was prepared from the dilution of 1,000 ppm (mg/L) As stock standard solutions. Concentrated HNO3 was obtained from Merck. Deionized water from Innovation Pure Water System (Human Corporation) was used throughout the study. An Arsenic Hollow Cathode Lamp was used for As detection. Absorbance was measured as the peak height at 193.7 nm with a spectral band pass of 0.5

nm. Five replicate measurements were performed using GFAAS for standard and sample solutions. The result of the hair analysis was given as ppb (µg/L) for As. The method presented in this study is sensitive and suitable for the detection of As in human hair at the low ppb level. The calibration curve was characterized by a high correlation coefficient (r = 0.9989). Furthermore, the GFAAS method was certified with the standard reference material CRM 397 (human hair), for the validation of the analytical method.

2.3. Electrocardiographic Recording and Measurements

A 12-lead resting ECG recording of each participant was obtained using Schiller AT-102 in the supine position, at rest, for at least 15 minutes, at a recording rate of 50 mm/sec. Measurements and interpretation of the QTc and the QTcd were performed by two electrophysiologists who were blind to the patients characteristics. In the case of an interobserver discrepancy (greater than 10%) of the measurements, a mean value of the two measurements was used. The QT interval was measured manually by the researchers from the beginning of the QRS complex to the end of the T wave and the corrected QT was measured using Bazzet's formula: QTc= QT / [RR]½. The QT dispersion was calculated as the difference between the longest and the shortest QT interval, on the 12 lead surfaces ECG.

2.3. Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS statistics 19, IBM). Minimum and maximum values, as well as mean ± standard deviation of continuous variables, were reported. Taking into consideration the sample size, an independent sample t-test was performed on samples to analyse differences between the groups. Pearson correlation coefficients were compared for As levels and the QT intervals. The confidence interval levels were chosen as 95% ($p<0.05$) and 99% ($p<0.01$).

3. Results

Table 1 demonstrates the significant differences in the QT max between healthy individuals and the subjects with high occupational As exposure (p = 0.039). The QT dispersion and As level in the hair samples also showed a significant difference between the study groups (p=0.002 and p=0.001, respectively).

Table 1. *Significant difference in the QT max between healthy individuals. (*p < 0.05 and **p < 0.01*)

Groups		**QTc max**	**QTc min**	**QTdisp**	**As (µg/g)**
Control	Mean ± S.D.	0.382 ±0.024	0.365 ±0.024	0.015 ±0.013	0.21 ±0.20
	Min	0.321	0.308	0	0.01
	Max	0.454	0.428	0.053	0.94
As-exposed workers	Mean ± S.D.	0.387 ±0.026	0.362 ±0.023	0.024 ±0.041	2.10 ±3.07
	Min	0.327	0.314	0	0.083
	Max	0.465	0.430	0.413	25.711
Total	Mean ± S.D.	0.385 ±0.026	0.364 ±0.024	0.0194 ±0.031	1.06 ±2.31
	Min	0.321	0.308	0	0.08
	Max	0.465	0.430	0.413	25.71
P		0.039*	0.342	0.002**	0.001**

The correlation between As levels in the hair samples and the QTc and the QTdis. A highly significant correlation was found between the QTcmax and the QTdis. ($r=0.788$; $p<0.01$ and $r=0.214$; $p<0.01$, respectively) A similar relationship between the QTc and the QTdisp parameters was determined ($r=0.211$; $p<0.01$). When the study population was grouped according to their occupational professions, fine grinding and drilling workers were found to have higher As levels (2.74 ± 3.46 ppm and 0.52 ± 0:45 ppm respectively, $p <0.001$), than the patients working in other industries.

4. Discussions

Occupational exposures to inorganic arsenic are associated with an increased mortality from cardiovascular disease [22, 23]. The most common means of arsenic exposure is in the arseniasis-endemic areas and through the ingestion of high-arsenic drinking water [24]. Morbidity and mortality from ischemic heart disease and cerebral infarction may be considered as late clinical manifestations of a long-term arsenic exposure, either by occupational or by drinking arsenic polluted water [1, 25, 26].

Arsenic exposure is accepted as an etiologic factor in type 2 diabetes and atherosclerosis. Means of exposure with drinking water is widely known, however, although exposure via aerosol is rare, it is also encountered. The QT interval represents ventricular depolarization and repolarization therefore it helps determine the period of mean ventricular action potential. In clinical practice, the corrected QT (QTc) allows the clinician to evaluate the QT interval regardless of the heart rate. The QTcdisp is a marker of heterogeneity and is frequently encountered in patients with a disparity in ventricular recovery. A long-term oral As2O3 exposure significantly increased the mean heart rate

and QTc interval and reduced the SDNN. However, the QT-interval, QT and QTc dispersions were not changed in a study conducted in a promyelocytic leukaemia population, in which patients were treated with oral As by Siu et al [27]. Furthermore, for indicators of pro-arrhythmic risks [16, 28], significant QTc prolongations of more than 30 milliseconds were observed at only a single time point (2 hours after oral As2O3), QTc prolongation never exceeded 50 milliseconds, and a QTc interval of more than 500 milliseconds was observed in only 3 patients within 4 hours of oral As2O3 administration [27]. Importantly, these observations were translated into absent ventricular pro-arrhythmia in all patients [27]. These results were superior to intravenous As2O3 administration, where 26 % of patients had QT intervals more than or equal to 500 milliseconds, with the QTc interval prolonged by 30 to 60 milliseconds in 36.6% of the patients during the treatment, and by more than 60 milliseconds in 35.4% of patients, resulting in torsades de pointes in 1% of cases.

In our study, As exposure was found to be related with ECG changes such as the QT dispersion. Possible occupational exposure to As may cause cardiac arrhythmias and sudden cardiac death. Further studies are needed to document the increased cardiac risk in populations with environmental and occupational exposure.

Author Statements:

- The authors declare that they have equal right on this paper.
- The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
- The authors declare that they have no-one to acknowledge.

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