Hypertension and Arsenic Exposure in Bangladesh

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Abstract—A prevalence comparison of hypertension among subjects with and those without arsenic exposure through drinking water was conducted in Bangladesh to confirm or refute an earlier observation of a relation in this respect. Wells with and without present arsenic contamination were identified, and we interviewed and examined 1595 subjects who were depending on drinking water from these wells for living, all ≥30 years of age. The interview was based on a questionnaire, and arsenic exposure was estimated from the history of well-water consumption and current arsenic levels. Of the 1595 subjects studied, 1481 had a history of arsenic-contaminated drinking water, whereas 114 had not. Time-weighted mean arsenic levels (in milligrams per liter) and milligram-years per liter of arsenic exposure were estimated for each subject. Exposure categories were assessed as <0.5 mg/L, 0.5 to 1.0 mg/L, and >1.0 mg/L and alternatively as <1.0 mg-y/L, 1.0 to 5.0 mg-y/L, >5.0 but ≤10.0 mg-y/L, and >10.0 mg-y/L, respectively. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg in combination with a diastolic blood pressure of ≥90 mm Hg. Corresponding to the exposure categories, and using “unexposed” as the reference, the prevalence ratios for hypertension adjusted for age, sex, and body mass index were 1.2, 2.2, 2.5 and 0.8, 1.5, 2.2, 3.0, in relation to arsenic exposure in milligrams per liter and millgram-years per liter, respectively. The indicated dose-response relationships were significant (P<0.001) for both series of risk estimates. These results suggest that arsenic exposure may induce hypertension in humans. (Hypertension. 1999;33:74-78.)

Key Words: body mass index ■ environment ■ epidemiology ■ arsenic ■ water consumption ■ risk factors ■ vascular diseases

A potentially devastating health crisis is unfolding in Bangladesh, where arsenic has leached from naturally occurring minerals into drilled wells.1–4 The immense scale of the human tragedy has only recently begun to attract attention from the world. Chronic ingestion of inorganic arsenic is known to cause characteristic skin alterations, such as hyperpigmentation (melanosis) and hyperkeratosis.5,6 There is also more or less good evidence that ingested arsenic may cause cancer of the bladder, liver, and other organs.6,7 In the past, sources of ingested arsenic have included Fowler’s solution, other medications, and arsenic-containing pesticides and defoliants. The main source of human exposure to inorganic arsenic is nowadays through drinking water, in most cases from natural contamination.

Recently, a study from Taiwan has shown an increased risk of hypertension with a dose-response relationship in a population that consumed arsenic-contaminated artesian well water.8 Exposure to arsenic in drinking water has also been reported as a risk factor for diabetes mellitus in Taiwan9 and Bangladesh.10 Diabetes mellitus related to occupational arsenic exposure has been observed in Sweden.11,12 Arsenic is known to cause blackfoot disease, a unique peripheral vascular disease that frequently ends with dry gangrene and amputation of the affected extremities.6 An atherosclerotic effect of arsenic has also been indicated, and peripheral vascular disease has been observed not only among individuals exposed to arsenic in drinking water13–16 but also among Moselle vintners chronically exposed to arsenic.6 Primary copper smelter workers with exposure to arsenic have altered blood vessel function and Raynaud’s phenomenon.17 Increased mortality from cardiovascular disease has been observed among copper smelter workers18 and art glass workers,19 both worker groups exposed to arsenic. An excess mortality from cardiovascular disease among residents in Taiwan, Chile, and Japan has been associated with environmental exposure to arsenic in drinking water.6

Existing reports on high arsenic levels in drinking water in Bangladesh and earlier epidemiological experience in this country20 led us to conduct the present study, which includes a comparison of the prevalence of hypertension among residents with and those without exposure to arsenic and also an elucidation of possible dose-response relationships.

Methods

Study Area and Subjects
Based on existing surveys of arsenic in drinking water (see below), 4 villages were selected from the districts of Faridpur, Nawabgong,
defined hypertension as a systolic blood pressure $\geq 140$ mm Hg combined with a diastolic blood pressure $\geq 90$ mm Hg, as used elsewhere.23 No other cut points were used with these data. Blood pressure was taken after rest and relaxation for at least 15 minutes in sitting position according to the protocol recommended by the World Health Organization.22 Blood pressure was measured 3 times, and the lowest value was taken as the proper value for this study. For the subjects who had hypertension, blood pressure was rechecked during 2 additional visits (once per visit). The mean of the systolic and diastolic blood pressures from these 3 occasions was used in the study and recorded as the closest multiple of 5. A mean blood pressure was also calculated as diastolic blood pressure plus one third of the pulse pressure, the latter being the systolic minus the diastolic blood pressure.

### Data Analysis

Data were stratified according to age (30 to 44, 45 to 60, and $\geq 60$ years of age), sex, and BMI; the respective BMI categories were $<19, 19$ to $22, \text{ and } \geq 22,\text{ respectively. Mantel-Haenszel–weighted prevalence ratios (MH-PR) with 95% confidence intervals (95% CI)}$ and a test of the dose–response relationship among the exposed were obtained by means of the Epi-Info package.\textsuperscript{23} A linear regression model was also applied regarding the mean blood pressure in relation to arsenic exposure in terms of both milligrams per liter and milligram-years per liter.

### Results

A total of 1481 adults (903 men and 578 women) had a history of arsenic exposure, whereas 114 (50 men and 64 women) were unexposed. The prevalence of hypertension increased in the middle-aged group (45 to 60 years) for men, but in women the higher prevalence was found in the age group $\geq 60$ years. The oldest subject participating was 85 years old.

Table 1 shows exposed and unexposed subjects according to age, sex, and BMI. The crude overall prevalence ratio (or risk) for hypertension amounted to 1.7 (95% CI, 0.8 to 3.3). After adjusting for age, sex, and BMI, the prevalence ratio was somewhat increased (MH-PR, 1.9; 95% CI, 1.0 to 3.6). The overall crude prevalence ratio for men was 2.1 (95% CI, 0.7 to 6.5), and for women 1.5 (95% CI, 0.7 to 3.4). After adjusting for age and BMI, the prevalence ratio for men slightly decreased, to 2.0 (95% CI, 0.6 to 6.1), but for women it increased (MH-PR, 1.8; 95% CI, 0.8 to 4.0).

As shown in Table 2, there was an increase of the prevalence ratio by increasing exposure, ie, 1.0, 2.0, and 2.5, using unexposed as the reference. After adjusting for age, sex, and BMI with the same reference, the prevalence ratios were somewhat increased, to 1.2, 2.2, and 2.5 for the exposure categories I, II, and III, respectively. This dose–response relationship was statistically significant ($P<0.001$).

When the different categories of milligram-years per liter of arsenic exposure were considered and adjustment was made for age, sex, and BMI, the prevalence ratios were 0.8, 1.5, 2.2, and 3.0 for the exposure categories $<1.0, 1.0 \text{ to } 5.0, >5.0 \text{ to } \leq 10.0, \text{ and } >10.0 \text{ mg-y/L}$, respectively, compared with those not exposed, and there was significant a dose–response relationship ($P<0.001$; Table 3).

In a linear regression model, which took into account age, sex, and BMI, there was an increase of the mean blood pressure by 3.40 mm Hg per mg/L and by 0.26 mm Hg per mg-y/L of arsenic exposure (data not shown). The increase in mean blood pressure in both series of exposure categories was statistically significant ($P<0.001$).
Discussion

The result of this study demonstrates a dose-response relationship between inorganic arsenic exposure from drinking water and risk of hypertension. Despite the lack of previous individual exposure data and the lack of information on potential confounders other than those we controlled for, the association seems strong enough to support the possibility of a causal association. There is also good agreement with the observations from Taiwan.8 Although there was no comprehensive, systematic sampling of the water supplies of the study area, the existing water measurements permit a reasonably good assessment of arsenic exposure. Furthermore, the effect of various unknown factors, such as use of bottled water, would dilute the effect and lead to an underestimation of the association. Because our study subjects were recruited from villages in which residents had similar occupations, socioeconomic status, lifestyles, and dietary habits, including salt intake, the variation among subjects of these potentially confounding variables is likely to be small.

Another aspect for discussion is that the procedure for recruiting subjects could have favored the participation of those who suffered from some disease. However, the subjects included in the study represent a very poor population of Bangladesh who are virtually without health care for diseases that are not directly life-threatening. This circumstance may explain why none of the interviewed subjects gave a personal or family history of hypertension or diabetes mellitus; also,
none were being treated with antihypertensive agents. Furthermore, hypertension is an asymptomatic disease and therefore is unlikely to influence the participation of the subjects; a selection bias is therefore unlikely in this respect. An observation bias is possible in so far as the observer could have had some idea of the exposure status of the subjects but not their level of exposure. It is therefore unlikely that an observation bias of this kind could have created the observed dose-response relationship, but a fully blinded situation for the examination would have been desirable. Application of various cut points to continuous variables such as blood pressure could lead to different results but would hardly create a dose-response relationship; however, here we applied only the cut points shown. The regression analysis, which requires no cut points, also indicated a dose-response relationship.

A potential confounding factor could also be the use of contraceptive pills. However, the use of pills rather than intrauterine devices is rare in rural Bangladesh, and it is unlikely that there would be any difference in this respect in relation to degree of exposure. The same argument of “no relation to the exposure” applies to physical activity and the 199 individuals who did not participate in the health examination. They were not available at the time of examination mainly because of work in the fields.

It is not known whether other contaminants (eg, other trace elements, such as sodium, magnesium, manganese, iron, mercury, chromium, lead, and fluoride) could be present in the water together with arsenic. However, there is no evidence of any remarkable presence of such trace elements in the study area, nor is it clear whether such elements would have any stronger influence on blood pressure.

Directly measured individual exposure over time would have been desirable. The estimated arsenic exposure obviously cannot include any time trends or likely fluctuations in the exposure depending on precipitation or other circumstances. Nor does it take into account the possibility that certain individuals for shorter periods of time might have used wells other than the usual one but not reported this in the interviews. The amount of water consumed by a person during different periods of his or her lifetime also remains unknown, and therefore it has not been possible to calculate more precisely the cumulative exposure to arsenic. These various limitations lead to uncertainty in assessment of exposure to arsenic, but there was no possibility other than to assume that current arsenic concentrations also are representative of the past. Despite these uncertainties, it is nevertheless reasonable to believe that the available water measurements were proper enough to create the broad exposure categories used in the analysis of the dose-response relationship.

Another limitation of this study could be that not all initially identified eligible subjects were available for the health examination. Socioeconomic status and occupations, especially farming, were found to be fairly similar between all participants, and we believe it is also valid for the nonparticipants because they belonged to interviewed families. There was indication of some slight positive confounding for men (the crude prevalence ratio exceeded the adjusted one), and negative confounding for women (the adjusted prevalence ratio exceeded the crude one), regarding age and BMI, as adjusted for (Table 1). It is unlikely, however, that more narrow categories of age and BMI would have made much of a difference in the risk estimates.

Long-term arsenic ingestion and development of hypertension has only recently been the subject of epidemiological studies, and the pathogenetic mechanism is unclear. However, peripheral vascular disease, ischemic heart disease, and hypertension have been reported in people who drank water with high arsenic concentrations in Taiwan. Inorganic arsenic induces blackfoot disease and ischemic heart disease, probably through a direct effect on the atherosclerotic process involving endothelial cells, smooth muscle cells, platelets, and macrophages. Arsenic has also been reported to induce renal insufficiency with cortical necrosis with hematuria, leukocyturia, and glycosuria. Arsenate has been found to inhibit the binding capability of the glucocorticoid receptor, to damage the endothelial barrier in the vascular systems, and perhaps to activate the leukocytes and platelets and also to initiate plaque formation. Whether arsenic may induce hypertension through any or several of these mechanisms needs further exploration.

Regarding lifetime exposure to arsenic in drinking water, a World Health Organization task group estimated that a concentration of 0.2 mg/L would result in a cumulative skin cancer risk of 5%. It is currently unclear whether the risk of getting hypertension from arsenic exposure is greater than or less than the cancer risk. To the best of our knowledge, there has been no other study outside Taiwan besides the current study on hypertension and arsenic exposure. The results of this study clearly corroborate the Taiwanese findings.

References


