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Lack of Effect of Drinking Water Barium on Cardiovascular Risk Factors

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Higher cardiovascular mortality has been associated in a single epidemiological study with higher levels of barium in drinking water. The purpose of this study was to determine whether drinking water barium at levels found in some U.S. communities alters the known risk factors for cardiovascular disease. Eleven healthy men completed a 10-week dose-response protocol in which diet was controlled (600 mg cholesterol; 40% fat, 40% carbohydrate, 20% protein; sodium and potassium controlled at the subject's pre-protocol estimated intake). Other aspects of the subjects' lifestyles known to affect cardiac risk factors were controlled, and the barium content (as barium chloride) of the drinking water (1.5 L/day) was varied from 0 (first 2 weeks), to 5 ppm (next 4 weeks), to 10 ppm (last 4 weeks). Multiple blood and urine samples, morning and evening blood pressure measurements, and 48-hr electrocardiographic monitoring were performed at each dose of barium. There were no changes in morning or evening systolic or diastolic blood pressures, plasma cholesterol or lipoprotein or apolipoprotein levels, serum potassium or glucose levels, or urine catecholamine levels. There were no arrythmias related to barium exposure detected on continuous electrocardiographic monitoring. A trend was seen toward increased total serum calcium levels with exposure to barium, which was of borderline statistical significance and of doubtful clinical significance. In summary, drinking water barium at levels of 5 and 10 ppm did not appear to affect any of the known modifiable cardiovascular risk factors.

Introduction

The current interim drinking water standards for the United States require that water systems have no more than 1 ppm (ppm = part per million = mg/L) barium in the drinking water they supply. This is not a problem for the many areas of the country that draw their drinking water from streams and lakes. However, many groundwaters include concentrations of barium higher than 1 ppm, and systems that use these groundwater sources may not meet the standards. Communities facing this problem exist in Illinois, Texas, Georgia, New Mexico, Kentucky, and Pennsylvania (*1*). In these areas, drinking water may contain as much as 10 ppm of barium, and lowering the barium content is difficult. Therefore it is important to know whether or not the interim drinking water standard of 1 ppm is necessary to protect humans against adverse health effects.

There are at least two reasons to believe that the interim drinking water standard of 1 ppm barium may be unnecessarily low (*2*). First, the standard was derived from inhalation data for barium because of the lack of data regarding human toxicity at low levels of exposure by ingestion (*3*). There are significant differences between inhaling barium and ingesting barium in drinking water, and there may be no relationship between the toxicity of inhaled barium and that of ingested barium. Also, the interim standard was developed using an assumption of 90% absorption of barium from drinking water (*3*). More recent work suggests that only 5 to 20% of barium is absorbed from drinking water (*4–7*). Thus, it may be reasonable to re-evaluate the barium drinking water standard of 1 ppm.

The Safe Drinking Water Committee of the National Research Council of the National Academy of Sciences has recommended that the barium standard be raised (*2*). Their 1982 analysis, which assumed a maximum gastrointestinal absorption of barium of 20%, suggested that a level of 9.4 ppm is safe. Their recommended standard is 4.7 ppm, which incorporates a safety factor of two. Therefore, we raise the questions: Is this recommendation reasonable? What data are available to assess the health effects of drinking water barium?

Three categories of health effects data exist for drinking water barium. The first type is human epidemiological data. At low concentrations (less than 1 ppm), several epidemiological studies have shown an inverse correlation between drinking water barium content and cardiovascular mortality (*8,9*). At these lower concentrations,

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cardiovascular death rates decrease as barium increases. Of course, water higher in barium tends to be higher in both calcium and magnesium (harder), so this finding may be confounded by other factors. In contrast, higher concentrations of barium (greater than 1 ppm), have been associated with higher cardiovascular mortality in one epidemiological study (*10*). An area of northern Illinois that has high drinking water barium concentrations (7–10 ppm) was compared with a nearby area that has low drinking water barium concentrations, and a higher cardiovascular death rate in the area with high barium concentrations was found. Another study in the same areas found no differences in blood pressure levels (*11*). These epidemiological studies have been criticized for failure to control for race, water softening, and other factors that are known to potentially affect the results. Thus, the epidemiological data on the health effects of drinking water barium are inconclusive at this time. Barium may have no effect, a beneficial effect, or an adverse effect on cardiovascular death rates.

The second type of data applicable to this issue is acute human toxicity experiences from accidental overdoses though it is difficult to apply overdose data to the chronic, low-dose situation. In large overdoses, barium causes cardiac arrythmias, hypokalemia, and hypertension as well as other effects (*1,12*). Toxic doses have been given also to animals and similar findings have been reported (*13*). Doses necessary to achieve these toxic effects in humans are approximately 500 ppm, assuming a 1-L ingestion (*1*).

The third type of data is derived from chronic low-dose administration of barium in drinking water to animals (*14–16*). In general, chronic exposure of rats to relatively high levels of barium in drinking water appears to have no deleterious effects. Minor changes in cholesterol, glucose, and urine protein were observed in one study (*15*), but there was no effect on mortality, growth, or other factors. Hypertension was seen at very high exposures in another study (*16*). Thus, chronic exposure of animals to barium at the same levels to which humans are exposed disclosed few apparent significant effects.

Overall, the data on the health effects of drinking water barium are incomplete, mixed, and inadequate. The purpose of this study, therefore, was to explore in humans the health-related effects, particularly those related to cardiovascular risk factors, of drinking water barium.

Patients and Methods

Eleven healthy male volunteers were studied using the protocol shown in Figure 1. The subjects' ages ranged from 27 to 61 years (mean 39.5 years; median 41 years of age). Four were black and seven were white. None of the subjects had hypertension, diabetes, or cardiovascular disease of any kind. They were on no medications during the course of the study. All provided informed consent, the protocol was approved by the University of Cincinnati Institutional Review Board, and the study was performed in the University of Cincinnati General Clinical Research Center (GCRC).

Week	0	1	2	3	4	5	6	7	8	9	10
Drinking water	1.5 L/day distilled			1.5 L/day 5 ppm barium				1.5 L/day 10 ppm barium			
Diet	Basal			Basal				Basal			
Lab studies			X			X					X
			SX			SX					SX
	S		UX		S	UX			S		UX
	X	X	UX		X	UX			X		UX
EKG monitoring			—			—					—

FIGURE 1. Study protocol. X, Lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides); apolipoproteins A1, A2, B; renal profile (Na, K, Cl, CO_2, BUN, creatinine, glucose); calcium, albumin. U, 24-hr urine for Na, K, VMA/metanephrines. S, CBC, urinalysis, hepatic/bone profiles. #, resting 12-lead EKG; 24-hr Holter monitor.

During the 10-week protocol, all food and beverages were provided by study staff, food was consumed in the GCRC, and subjects were instructed not to eat or drink anything other than what was provided. During the first 2 weeks, the drinking water (1.5 L/day) consisted only of distilled water. During the next 4 weeks, the drinking water (1.5 L/day) contained 5 ppm barium in the form of barium chloride. During the last 4 weeks of the study, the drinking water (1.5 L/day) contained 10 ppm barium. Subjects were permitted to drink additional distilled water after consuming the mandatory 1.5 L of study water if they so desired.

All drinking water was distilled and charcoal-filtered to remove trace impurities. A concentrated solution of barium chloride, prepared weekly, was diluted with distilled water to the appropriate concentration on a daily basis. An aliquot of drinking water prepared in this way was tested daily for barium content, and these measures confirmed that the subjects' drinking water contained the specified barium concentrations. Strict recording of mandatory water intake as well as optional water intake was maintained throughout the protocol.

The subjects' diets were strictly controlled during the course of the study. The diets consisted of 20% protein, 40% fat, and 40% carbohydrate. The polyunsaturated: saturated ratio for fats was 0.4. The diet contained 600 mg of total cholesterol daily. Sodium and potassium were strictly controlled throughout the 10 weeks at levels consistent with the subject's pre-protocol intake. Thus, this diet was fairly typical of the American diet, though it was slightly more atherogenic (higher in cholesterol and saturated fat) than current dietary practices. Sodium and potassium intake were regulated at usual levels for each subject. The barium content of the diet was unknown. However, the barium content of a typical hospital diet has been measured previously elsewhere and found to be about 0.75 mg/day (*17*). Thus, the amount of barium in the diet probably was small relative to the amount

ingested in the drinking water during the study periods (7.5 mg and 15 mg/day, respectively, for the 5-ppm and 10-ppm periods).

Other factors known to affect cardiovascular risk were controlled as well. Subjects were asked to perform the same amount of exercise during the entire 10 weeks of protocol. They were allowed to smoke, but if they were smokers they were instructed to smoke consistently throughout the protocol, and this was monitored by patient diary on a daily basis. Subjects were instructed not to consume any alcohol. They continued their usual daily working schedule and were allowed to sleep at home overnight.

Multiple data items were collected as illustrated in Figure 1. Blood was collected at admission and periodically throughout the protocol. However, the main end points were four consecutive daily samples at the end of each of the three study periods (0, 5, 10 ppm). Blood was obtained at this time for plasma total cholesterol, triglycerides, and HDL cholesterol; apolipoproteins A1, A2, and B; serum potassium and glucose; and serum calcium and albumin. Two 24-hr urine collections were performed at the end of each study period for measurement of sodium and potassium content and vanillymandelic acid (VMA) and total metanephrines. LDL cholesterol was calculated as total cholesterol minus HDL cholesterol minus triglycerides/5. Corrected (for albumin) calcium levels were calculated as total calcium minus albumin plus 4.

No attempt was made to determine barium levels in serum or to measure the absorption of the barium in the drinking water. Because barium is cleared rapidly from serum via deposition in bone (*18,19*), attempts in the past to measure serum levels chemically after oral intake in animals have been unsuccessful (*14*). Such measurements require radioisotope methods that were outside the scope of this study.

Electrocardiograms and 24-hr continuous electrocardiographic monitoring were performed on 2 consecutive days at the end of each study period. The principal end points from the electrocardiographic monitoring were the standard cardiac cycle intervals (PR, QRS, and QT intervals) and any arrhythmias detected by the 24-hr monitoring including indices of ventricular irritability such as premature ventricular contractions.

In addition to the primary end points described above, safety tests including complete blood counts, urinalyses, and liver function tests were performed periodically as shown in Figure 1.

The lipid tests described above were performed using Centers for Disease Control (CDC) standardized methodology (*20,21*). The apolipoprotein studies were also performed using recognized methods in the same laboratory (*22,23*). The remaining blood tests were performed by standard procedures in the University of Cincinnati Hospital laboratory. Electrocardiographic measurements and interpretations were provided by study staff and hospital cardiologists who were unaware of the study design or intent.

Laboratory test results were analyzed by a two-way analysis of variance technique using subject and dose by standard SAS procedures. Each cell in the two-way ANOVA consisted of the mean of the four (or two) samples obtained at the end of each study period. The EKG intervals were analyzed in a similar fashion. The number of premature atrial and ventricular contractions were analyzed similarly, although the other findings of the 24-hr electrocardiographic monitoring required qualitative interpretation.

Results

Results of the principal outcome variables measured in this study are shown in Table 1. With exposure to barium there was no change in either morning or evening systolic or diastolic blood pressures. Similarily, there was no change in total cholesterol, triglycerides, HDL cholesterol, or calculated LDL cholesterol. Apolipoproteins A1, A2, and B were unchanged. Serum potassium and glucose did not change through the protocol. Urine metanephrines also did not change and urine VMA showed no consistent change with increasing barium dose suggesting that the observed difference at 5 ppm was because of chance.

There was a trend towards increased total serum calcium between 0 and 5 ppm that persisted at 10 ppm. Since about half of the total calcium in the blood is bound to protein, primarily albumin, we further evaluated this borderline finding by calculating a corrected calcium level that is normalized for differences in albumin level. This calculation revealed an apparent statistically signifi-

Table 1. Summary data.

Outcome variable	Study period 0 ppm	5 ppm	10 ppm	ANOVA *p* value
AM systolic BP, mm Hg	117	117	117	0.94
AM diastolic BP, mm Hg	77	76	75	0.28
PM systolic BP, mm Hg	120	117	118	0.35
PM diastolic BP, mm Hg	77	76	76	0.42
Total cholesterol, mg/dL	193	195	192	0.79
Triglycerides, mg/dL	80	87	80	0.07
LDL-C, mg/dL	127	128	126	0.73
HDL-C, mg/dL	50	49	51	0.32
LDL:HDL ratio	2.80	2.86	2.67	0.10
Apo B, mg/dL	114	121	119	0.27
Apo A1, mg/dL	130	128	127	0.58
Apo A2, mg/dL	46	45	44	0.42
Potassium, mEq/L	4.12	4.18	4.21	0.17
Glucose, mg/dL	89	90	88	0.46
Calcium, mg/dL	9.11	9.23	9.23	0.08
Albumin, gm/dL	4.25	4.20	4.19	0.15
Corrected calcium[a]	8.86	9.03	9.01	0.01
Urine metanephrines, μg/mg Cr	0.21	0.22	0.26	0.39
Urine VMA, μg/mg Cr	2.48	1.96	2.44	0.02
Heart rate, beats/min	71	71	71	0.99
PR interval, sec	0.16	0.17	0.17	0.08
QRS interval, sec	0.10	0.10	0.10	0.63
QT interval, sec	0.37	0.37	0.37	0.79
PAC's, per hr	0.9	7.3	1.3	0.16
PVC's, per hr	0.26	0.19	0.05	0.46

[a]Corrected calcium = total calcium − albumin +4.0

cant increase in total calcium, which was attributed to a slight decrease in serum albumin during the course of the study. The absolute magnitude of this change is quite small and would not be expected to be clinically important.

The cardiac cycle intervals by electrocardiography were unchanged throughout the study. In particular, the QT interval and the QT interval corrected for heart rate (not shown) did not shorten with exposure to barium. Increases in serum calcium typically shorten the QT interval, and the lack of any shortening supports our belief that the borderline increase in calcium was not clinically significant.

There were no significant arrhythmias noted when the subjects were exposed to barium. There was no increase in ventricular irritability, as manifested by the number of premature ventricular contractions during prolonged monitoring. Similarily, there were no apparent conduction problems. The number of premature atrial contractions did increase somewhat during the 5 ppm barium exposure period, but this was not statistically or clinically significant. One subject had several brief runs of ventricular tachycardia during the monitoring at the end of the distilled water period. Ventricular tachycardia is a potentially serious arrythmia, though when it is found in subjects without other apparent heart disease, it is not usually of major consequence. No subsequent ventricular tachycardia was noted in this subject during either of the barium periods.

Discussion

In this study, the exposure of 11 healthy men to barium in drinking water at concentrations of 5 and 10 ppm did not result in any apparent changes in modifiable cardiovascular risk factors. Specifically, there was no increase in blood pressure, cholesterol or triglyceride levels, or glucose or potassium levels. There was no detectable effect of barium on catecholamine metabolism that could result in high blood pressure or serious arrhythmias. Furthermore, direct monitoring of heart rhythm showed no impact on several indices of cardiac irritability and arrhythmia potential.

There was a trend toward slightly increased total calcium in the blood. This increase in total calcium could not be explained by increases in blood protein levels. When the total calcium was corrected for changes in albumin levels, the trend toward the increase became statistically significant. However, the magnitude of the change was very small and could not be implicated as a factor increasing cardiovascular risk. It should be noted, also, that multiple comparisons were made by design in this study. Thus, the chances of showing a statistically significant change in a single variable at an alpha level of 0.05 are greater than 50% by chance alone. Moreover, work in animals has not shown any change in serum calcium with exposure to barium (*14*). Thus, this apparent change in total calcium should be viewed only as an isolated finding worthy of future research specifically designed to confirm whether or not a change in calcium metabolism occurs in people or animals consuming barium in their drinking water.

A number of limitations of this study should be mentioned. First, because we studied only 11 healthy men, it is possible that a true effect was unrecognized because of the small numbers of subjects or because the subjects were healthy. However, in a similar study involving drinking water chlorine and cholesterol metabolism, a change of only 3% in total cholesterol level was shown to be statistically highly significant (*24*). The design of this trial makes each subject his own control, thus making it possible to detect very small changes in outcome variables. Obviously, it is possible that people with cardiovascular disease or cardiovascular risk factors might be affected differently by barium than healthy men would be. We cannot exclude this possibility though this study provides no data to support it.

A second potential limitation is the relatively brief exposure interval. The baseline period was only 2 weeks long because all of the subjects were consuming Cincinnati drinking water which, because it is drawn from the Ohio River, is very low in barium. Also, there was no need for a significant washout period. The study intervals were also relatively brief (4 weeks), though most drugs and dietary changes that affect cardiovascular risk factors manifest those effects within a month of initiation. Even so, we cannot exclude the possibility that exposure to barium for years would produce effects, whereas short-term exposure did not.

A third potential limitation is the lack of data on absorption of barium or serum levels in these subjects, as discussed earlier. However, there is no reason to suspect that their absorption or serum levels would be any different than that of other adults exposed chronically to drinking water barium in this country.

This study contributes to the aforementioned literature on the health effects of barium in the following ways. First, it appears that toxic effects of ingested barium, such as hypertension and hypokalemia observed at high doses, are not seen at the lower concentrations, which may be found in drinking water supplied to humans. Because toxic effects of overdoses of barium are seen acutely, an analogous effect at lower doses should have appeared in this study if it truly existed. Second, this study confirms the generally negative studies performed in rats. Naturally, this study does not provide any mortality data to support or refute the epidemiological data on this subject, though it suggests that any impact of drinking water barium on cardiovascular disease does not occur through the known modifiable cardiovascular risk factors. This protocol studied drinking water barium concentrations of 5 and 10 ppm. The negative findings support the findings of the Safe Drinking Water Committee at the National Research Council that drinking water barium is probably safe for human consumption up to a concentration of 9.4 ppm and that raising the standard to 4.7 ppm (with a safety factor of 2) might be reasonable.

In summary, this study, performed under carefully defined experimental conditions, did not show any significant impact of drinking water barium at 5 and 10 ppm on the known modifiable cardiovascular risk factors. A trend towards increased serum calcium was observed though this finding needs to be confirmed by other studies specifically designed for that purpose.

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