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The Effect of Drinking Water with a High Content of Antimony and Arsenic on the Dynamics of their Distribution in the Kidneys and the Renal Excretory Function in Rats

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Abstract

This article is devoted to the study of the dynamics of antimony accumulation in renal tissue and the assessment of the renal excretory function in Wistar rats following a subchronic 90-day experiment with consuming model water from a man-made reservoir formed at a gold mining plant with a different ratio of subthreshold and threshold concentrations of arsenic and antimony. It is shown that the dynamics of the distribution of antimony ions in the renal tissue of rats is determined by the exposure time and the ratio of concentrations of these ions in water. Depending on this, the nephrotoxic effect, characterized by changes in diuretic, ionuretic, and osmoregulatory functions, manifests itself in different ways - increased fluid excretion and decreased ionuresis; absence of changes in urination and increased osmolality and natriuresis, or decreased excretion of osmotically active substances at different times of chronic intoxication formation. Changes in renal function are not detected at rest on an empty stomach, but manifest themselves only under conditions of a water load test (3% of body weight), when it is necessary to activate reserve mechanisms for regulating the water-salt balance.

Thus, for the first time in warm-blooded animals, the spectrum of manifestations of the nephrotoxic effect is shown in conditions of prolonged consumption of drinking water with a different ratio of subthreshold and threshold concentrations of arsenic and antimony.

Keywords: Antimony; Arsenic; Model Drinking Water; Renal Excretory Function; Ion Distribution in Renal Tissue

Introduction

The effect of acidic drainage waters from mining waste sites on water subjects has been the subject of study for many years not only by Russian [1-5], but also by foreign researchers [6-10]. This problem is of particular importance for some regions of Siberia, due to the large volumes of accumulated mining waste, which are sources of contamination of drinking and cultural water use facilities with toxic elements and serve as a significant risk factor for public health [1,2,10]. On the territory of one of Siberia regions, a man-made lake was formed from the hydraulic dump of a gold extraction plant, which is used by the local population for household purposes. At the same time, water from this lake enters the groundwater horizons, affecting the quality of drinking water supply in the village [2]. Depending on the location of the water intake, the content of many elements exceeded the permissible limits, but the greatest excess was determined for arsenic and antimony. [1,2]. It is known that the negative effects of arsenic and antimony on the body are due to their selective ability to bind to thiol groups that are part of biomolecules, and, as a result, blocking of active centers, leading to disorders of many functions in the body [11,12]. Studies have shown the relationship between the development of pre-pathological (pathological) conditions and the accumulation of these elements in tissues and organs [1,13, 14].

According to the results of [15,16], one of the main organs of arsenic deposition is the kidneys, therefore it is a recognized nephrotoxic metalloid that triggers various processes inside cells (for example, depletion of intracellular glutathione, an increase in free radicals in the cells, which in turn causes inflammation and apoptosis) [17,18]. In acute poisoning, protein and fatty degeneration of the convoluted tubules develops, and in chronic intoxication, tubule injury and various forms of renal dysfunction develop [17,19,20]. Trivalent arsenic compounds are excreted from the body mainly by the intestine, and pentavalent compounds are excreted by the kidneys [21].

Antimony is also found in many organs, and the nature of its distribution is the same regardless of the route of entry into the body [14]. The absorption of antimony is higher than that of arsenic, which implies a higher elimination value. The study [14] showed that the deposition of antimony is observed mainly in the blood, and the content of the element in organs and tissues is significantly lower, sometimes even the threshold for determination. As toxicity is caused by increased formation of reactive oxygen species (ROS), which cause oxidative damage in the kidneys [22,23]. One of the biomarkers of acute kidney injury is NGAL (neutrophil gelatinase–associated lipocalin), a protein of the lipocaine family caused disorders in the Shumlyansky-Bowman capsule and in the epithelial cells of the proximal convoluted tubules [19]. These changes could be related to the excessive accumulation of As and its metabolites in the renal tissue. Administration of pentavalent antimony compounds to rodents led to a significant decrease in urine osmolality, increased urination, and changes in clearance, which is associated with glomerular-tubular balance disorders [14,24]. Antimony elimination is complementary to the valence of the element in the compound. Thus, when Sb_2O_3 (Sb III) was added to rat food, 80-100 micrograms were excreted daily in the urine, and up to 100 mg of the element was excreted in the faeces. Pentavalent antimony (Sb V) is excreted mainly in the urine, even when enters into the stomach [19, 21].

Despite many studies on the deposition of arsenic and antimony in the body with their excessive intake [6,10,12,14,15,16,21], their toxic effect on the kidneys [11,17,18,19,20,22,23], the dynamics of their deposition in the organ, depending on the concentration, is still unclear, and also the changes in the excretory function of the kidneys during the accumulation of these elements in the body are not examined.

The present work is devoted to the study of some of these issues. The aim is to study the dynamics of antimony distribution in the kidneys under conditions of prolonged consumption of drinking water with different concentrations of antimony and arsenic, as well as to assess the functional state of the kidneys as one of the target organs of the nephrotoxic effect of these elements.

Tasks- to determine the changes in antimony concentrations in rat kidneys under the conditions of a 90-day subchronic test when drinking water containing different amounts of antimony and arsenic is consumed; to evaluate the excretory function of the rat kidneys in the dynamics of the experiment both at rest and after a water load test at the end of the observation period.

Scientific novelty and theoretical significance: for the first time, the dynamics of the distribution of antimony ions in the renal tissue of rats following 90-day consumption of model water with different ratios and concentrations of antimony and arsenic is shown, and their effect on the renal excretory function at rest in the morning on an empty stomach and after water load is described, which makes it possible to assess the functionality of the excretory system.

Practical significance: The data obtained will provide information on the nature of the public health hazard associated with the subchronic effects of antimony and arsenic contained in drinking water.

Materials and Methods

The white male Wistar rats weighing 250-300 g were the object of the study. After admission to the toxicology laboratory, they underwent 10-day quarantine and adaptation in the same type of conditions on a standard diet and free access to water. Groups for studying the accumulation of antimony in the kidneys and assessing kidney function were formed using random numbers based on body weight as the leading indicator.

For 90 days, experimental animals received model water for drinking, prepared by sequentially diluting water from a man-made reservoir formed at the gold extraction plant's tailings pond, which contained arsenic and antimony salts in the following concentrations: group 1 - 0.15 and 0.68 mg/dm3, respectively; group 2 - 0.05 and 0.227 mg/dm3; group 3 - 0.016 and 0.075 mg/dm3; group 4 – 0.0055 and 0.025 mg/dm3. The control group received drinking water from the municipal water supply, the concentration of arsenic in which was 0.01, antimony less than 0.005 mg/dm3. The content of zinc, lead, copper, manganese, calcium, iron, barium, aluminum and strontium in the drinking water of the animals of the experimental and control groups did not differ significantly.

During the experiment, on days 7, 14, 40, 70 and 90, part of the animals of the experimental groups (n = 3 at each stage) after anesthesia with intraperitoneal administration of nembutal at a dose of 4 mg /100 g of body weight was subjected to autopsy to take samples of renal tissue in order to determine the antimony content. The dynamics of antimony accumulation in kidney tissues was evaluated using an AA-7000 Shimadzu atomic absorption spectrometer using an auto-dispenser. The method is based on measuring the absorption of radiation of a resonant wavelength by atomic vapor of the element being determined, formed as a result of electrothermal atomization of the analyzed sample in a graphite furnace of the spectrometer. A total of 72 kidney samples were examined.

The results of the arsenic content in the kidneys were judged by data obtained under similar conditions and presented in the articles [1,14].

Given that antimony (Sb) is close to arsenic in its properties and mechanism of action, having a depressing effect on enzymes involved in carbohydrate, fat, and protein metabolism [12,13,14,25,26], it is very important to study the nature of the combined toxic effect of these elements on kidney function. In this regard, before priming, on the 40th and 90th days of follow-up, the functional state of the kidneys was assessed at rest in the morning on an empty stomach. In addition, on the 90th day of the experiment, all animals were tested with a water load - the excretory function of the kidneys was determined by oral intake of 30 ml/kg of drinking water [27]. On the days of the experiment, rats were weighed in the morning and placed in exchange cages without access to food and water, and background urine samples were collected for 3 hours for further analysis. During an aqueous functional test, all rats were given 3% of their body weight in the form of tap water orally through a probe after collecting background urine samples. Urine samples were collected within 2 hours after fluid intake. In the collected urine samples, its quantity, osmolality (Uocm, by cryoscopy using Osmomat milliosmometer, Germany), and the concentration of Na+ and K+ ions were determined by flame photometry (BWB-XP Flame Photometer, Great Britain). Based on the data obtained, the excretory function of the kidneys was evaluated according to generally accepted indicators: minute diuresis (V), excretion of sodium, potassium ions and osmotically active substances (UNaV, UKV, UocmV) [27,28].

Statistical data processing and plotting were performed using the Statistica 10.0 software package using the Student's t-test for independent samples. The differences were considered significant at $p < 0.05$.

Results and Discussion

The results of a study of the accumulation of antimony in kidney tissues when it enters the body of male Wistar rats with drinking water in 4 different concentrations over a 90-day oral exposure are presented in Table 1.

Control points of the study, day	Groups of experimental animals			
	1	2	3	4
7-th	0,460±0,002***	0,325±0,005	0,134±0,006	0,098±0,001
14-th	0,479±0,020 **	0,416±0,028*	0,228±0,013	0,416±0,028*
40-th	0,496±0,008***	0,251±0,005	0,118±0,005	0,294±0,004
70-th	0,551±0,041***	0,387±0,003	0,162±0,002	0,144±0,004
90-th	0,582±0,022***	0,401±0,002*	0,109±0,002	0,108±0,022
The control group on day 90 (n= 12)	0,346±0,015	0,346±0,015	0,346±0,015	0,346±0,015

Table 1: Average concentrations (M±m) of antimony in the renal tissue of experimental rats of the 1st, 2nd, 3rd and 4th experimental groups at various stages of the subchronic 90-day experiment, in mcg/g.
Notes: here and in the following tables there are significant differences from the control data: * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Table 1 shows that the concentration of antimony in the kidney tissues of group 1 rats was significantly (1.3-1.7 times, $p<0.01$ - $p<0.001$) higher than the level of the control group during all examination periods. In the 2nd experimental group, the concentration of antimony in kidney tissues exceeded the control level on days 14 and 90 (by 1.2

times, $p<0.05$), and on day 40 it was lower; in groups 3 and 4, the concentrations of this metalloid were significantly lower and only on the 14th day of the experiment in the 4th group exceeded the control level (1.2 times, $p<0.05$).

The lower antimony content in the kidneys in the 3rd and 4th experimental groups compared with the control can be explained by the fact that both arsenic and antimony mainly accumulate in the blood, and in organ tissues the antimony content is often below the detection limit [14], which is due to the low ability of antimony compounds to be absorbed into the body from digestive tract [29], as well as comparable or lower consumption of arsenic with water in these groups compared to the control, which could affect a decrease in the level of antimony deposition in the kidneys.

This assumption is confirmed by data on the average intake of antimony and arsenic during the experiment. The average daily doses of antimony and arsenic ingestion with water into the body of animals of the 1st, 2nd, 3rd and 4th groups were calculated based on the results of a study of actual water consumption. From the Table 2 it can be seen that during the 90-day subchronic experiment, the daily dose of metalloids received with water by animals progressively decreased from the 1st to the 4th experimental groups. The intervals between the tested levels of oral exposure to antimony and arsenic approached an arithmetic progression and statistically significantly differed from each other.

Control points of the study, day	Groups of Experimental Animals							
	1		2		3		4	
	Sb	As	Sb	As	Sb	As	Sb	As
7-й	63,60	14,10	17,91	3,95	6,22	1,32	1,56	0,34
14-й	109,24	24,10	22,01	4,85	7,05	1,50	2,61	0,57
40-й	64,41	14,80	22,46	4,95	6,62	1,41	2,37	0,52
70-й	87,66	19,34	17,86	3,93	5,15	1,10	1,56	0,34
90-й	123,92	27,33	11,85	2,61	2,85	0,61	0,95	0,21
The average dose, M±m	89,79±	19,93±	18,42±	4,06±	5,58±	1,19±	1,81±	0,40±
	11,99	2,58	1,91	0,42	0,75	0,16	0,30	0,07
Minimal	63,6	14,1	11,85	2,61	2,85	0,61	0,94	0,21
Maximum	123,9	27,33	22,46	4,95	7,04	1,50	2,61	0,57

Table 2: Doses of antimony (Sb) and arsenic (As) ingested by animals of the experimental groups with drinking water at various times of subchronic exposure, in micrograms / kg/day.

Since both semimetals have a nephrotoxic effect [11,17,18,19,20,22,23], it was important to assess the functional state of the kidneys in the middle and end of the period of subchronic priming with the previously indicated doses of antimony and arsenic.

Table 3 shows the results of a study of kidney function in experimental animals compared with the control group before priming, 40 and 90 days after drinking water consumption with different concentrations of the analyzed elements.

Indicators	Before the Seed					On the 40th Day After the Seed (Background)				
	1	2	3	4	К	1	2	3	4	К
V, ml/min.100g	0,05 ± 0,01	0,04 ± 0,01	0,05 ± 0,01	0,07 ± 0,01	0,06 ± 0,01	0,07 ± 0,01	0,07 ± 0,01	0,08 ± 0,01*	0,06 ± 0,01	0,06 ± 0,01
$U_{Na}V$, mcM/min.100g	3,5 ± 0,6	7,1 ± 1,1	4,3 ± 0,4	5,4 ± 0,5	4,8 ± 0,5	34,2 ± 2,0 *	34,1 ± 2,4 *	55,2 ± 6,6	31,2 ± 4,3	49,0 ± 5,8
U_KV, mcM/min.100g	16,6 ± 1,3	18,1 ± 1,9	21,1 ± 1,4	22,9 ± 1,0 *	18,7 ± 1,8	260,5 ± 14,5***	274,6 ± 16,7***	468,2 ± 41,7	400,9 ± 21,3	452,1 ± 20,6
Uosm, mosm/L	2395 ± 185	2667 ± 268	2782 ± 339	2474 ± 161	2802 ± 202	2642 ± 136	2994 ± 163	2124 ± 202**	2624 ± 119	3001 ± 202

Uosm.V, mosm/min.100g	120 ± 19	107 ± 6**	139 ± 9	173 ± 8	168 ± 19	185 ± 14	209 ± 12	169 ± 15	157 ± 13	180 ± 21
	On the 90th Day After the Seed (Background)					**On the 90th Day After the Seed and 3% Water Load**				
	1	**2**	**3**	**4**	**К**	**1**	**2**	**3**	**4**	**К**
V, ml/min.100g	0,06 ± 0,01	0,06 ± 0,01	0,07 ± 0,01	0,05 ± 0,01	0,07 ± 0,01	0,16 ± 0,02***	0,36 ± 0,02**	0,30 ± 0,02	0,42 ± 0,01***	0,28 ± 0,02
$U_{Na}V$, mcM/min.100g	27,9 ± 1,9**	20,2 ± 3,1	17,3 ± 2,5	15,4 ± 3,2	19,2 ± 1,3	2,2 ± 0,2	0,9 ± 0,2***	1,3 ± 0,5*	1,1 ± 0,4***	2,7 ± 0,2
U_KV, mcM/min.100g	198,5 ± 16,3	162,9 ± 12,1	174,3 ± 28,2	133,6 ± 7,3	182,7 ± 17,8	24,2 ± 2,0***	30,9 ± 2,8***	90,3 ± 7,7	38,6 ± 4,9 **	76,4 ± 5,1
Uosm, mosm/L	2096 ± 113*	1911 ± 111**	2087 ± 175	1995 ± 141*	2396 ± 73	356 ± 25**	233 ± 8***	340 ± 33	177 ± 12***	278 ± 7
Uosm.V, mosm/min.100g	126 ± 12*	115 ± 7**	146 ± 18	99 ± 7***	167 ± 13	70 ± 10	84 ± 7	102 ± 8*	74 ± 4	78 ± 6

Table 3: Indicators of excretory kidney function of white Wistar rats on the 40th and 90th days of water consumption with increased concentrations of antimony and arsenic (M±m). Note: 1, 2, 3, 4 are experimental groups of animals, K is the control group. Significant differences from the control group of animals: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. After water intake, all indicators of renal function significantly differ from the background values on the 90th day of the experiment.

As can be seen, there were practically no significant differences between the indicators of kidney function between all groups, including the control group, before the start of the seed, which indicates the same functional state of the kidneys of the rats selected for the study.

However, on the 40th day of follow-up, the diuresis in rats of the 3rd experimental group was significantly higher than in the control one. The revealed state of polyuria is probably a manifestation of the compensatory and adaptive reaction of the body to the combined toxic effect caused by the need to excrete an excessive amount of ions.

In parallel with the tendency to increase urination, there was a significant decrease in the excretion of sodium and potassium cations in the first two groups, whereas in the 3rd and 4th experimental groups, the excretion of these cations corresponded to the control level. Nonlinear dependences of effects on antimony and arsenic doses associated with the involvement of adaptive and compensatory reactions in the pathogenesis of chronic intoxication are consistent with fundamental patterns known in toxicology and indicate that the data obtained are not random [30]. The described changes naturally affected urine osmolality – there was a tendency for it to decrease in groups 1 and 2, however, due to increased diuresis, the total excretion of osmotically active substances remained at the level of the control group of animals.

Thus, 40 days after the start of taking water with elevated concentrations of antimony and arsenic in different ratios, there was a change in the diuretic and ionuretic functions of the kidneys, mainly in the first three experimental groups, a slight increase in urination and a decrease in the excretion of potassium and sodium, which generally did not affect the level of excretion of osmotically active substances. It is logical to assume that the diagnosed variant of the restructuring of the excretory function of the kidneys is due to the need of the animal body for the excretion of toxicants due to increased diuresis and decreased ionuresis.

On the 90th day after the start of priming, the background level of diuretic and ionuretic kidney function in all experimental groups practically did not differ from the control, which may indicate the adaptation of the kidneys to the intake of water with an excess of antimony and arsenic salts.

At the same time, a decrease in osmoregulatory function was observed, which manifested itself in a decrease in urine osmolality and excretion of osmotically active substances in all experimental groups, correlating with the levels of antimony accumulation in kidney tissues. Perhaps this indicates latent kidney damage, which can become chronic as a result of consuming water with high levels of antimony and arsenic.

To determine the reserve capabilities of kidney function, stress tests are usually used, which make it possible to identify latent disorders that often do not manifest themselves in normal comfortable conditions, for example, on an empty stomach [27]. For this purpose, after collecting background urine samples, we gave all animals a 3% body weight water load in the form of ordinary tap water through a probe.

The first you should pay attention to (Table. 3), animals of all groups developed a polyuric reaction characteristic of healthy animals – increased diuresis, decreased ion excretion and osmolality, which is necessary to restore the body's water-salt homeostasis [31].

Therefore, all indicators of the renal reaction significantly differed from the background values. However, when comparing the kidney response to water load in experimental animals compared with control rats, it can be seen that in group 1, the levels of diuresis and ion excretion were lower than in control, although osmolality exceeded control values; in group 2, urine and ion excretion, as well as osmolality, were significantly lower than control; in group 3, there were no significant differences from control rats; and in group 4, as well as in group 2, renal excretory function was lower than in the control.

This confirmed the accumulation of a nephrotoxic effect on day 90, the totality of which was clearly manifested when using a water load that required the activation of the reserve capabilities of the kidneys. The most pronounced changes in renal function were observed in the 1st, 2nd and 4th experimental groups and were multidirectional. The diuretic effect and the intensity of potassium excretion by the kidneys of rats in the experimental groups generally decreased with increasing exposure to antimony and arsenic and reached a minimum in group 1, in which urine osmolality significantly increased. The opposite trend was revealed when analyzing the dependence of the level of sodium excretion on exposure to antimony and arsenic. In general, the quantitative characteristics of the excretion of leading ions by the kidneys of rats in the experimental groups demonstrated nonlinear dose-dependent toxicokinetics in conditions of impaired renal ion-regulating function by the studied elements. At the same time, stress tests requiring the inclusion of compensatory mechanisms for homeostasis stabilization revealed a set of pathogenetically significant qualitative changes of renal function, assessed from the standpoint of harmfulness criteria.

Conclusion

Currently, it is considered correct to evaluate the effects of exposure to mixtures of chemicals of constant composition at levels and below the maximum doses of individual components [32]. In this regard, to assess the nephrotoxic effect of antimony and arsenic entering the body of experimental animals with drinking water, 4 exposure levels were tested, the first and second of which, according to the literature, exceed the thresholds of chronic oral action, the third was close to the threshold, the fourth was a subthreshold [33,34]. An important task of the experimental study of target mixtures is to determine the "similarity" of their components [35]. The coincidence of qualitative changes in the totality of the studied indicators in the experimental groups indicated a homogeneous nephrotoxic effect of antimony and arsenic [36]. A more difficult task was to assess the type of combined toxic effect of the components of a binary mixture, which can be determined by the sum of the scaled exposure levels of the individual components of the mixture or the sum of the effects. Calculations of the coefficients of additivity (k), taken as a quantitative measure of the combined effect of the components of the mixture [35,36] showed that when antimony and arsenic were injected into the body of rats of the 4th experimental group in subthreshold doses, more than an additive effect on kidney function was recorded, and when they approached the threshold levels in the 3rd experimental group, a partial summation of the effects of exposure was recorded. When the rats of the 1st and 2nd experimental groups were exposed above the threshold levels, the k coefficients did not reach unity, which characterizes the less than additive (independent) effect of antimony and arsenic on the state of renal functions. According to the results of the experimental study, on the 40th day of exposure of animals of the 1st and 2nd experimental groups to a mixture of antimony and arsenic, there was a significant decrease in the excretion of sodium and potassium relative to the control group, which may serve as a sign of the development of a nephrotoxic effect. In rats of the 3rd main group exposed to a model mixture of antimony and arsenic in average daily doses permissible daily intake rates up to 6 and 2 mcg/kg (TDI), [32,33] during this period of examination, a significant increase in diuresis and a decrease in urine osmolarity were diagnosed relative to the control. The increased diuretic effect in this group when using such daily doses of the elements indicated a threshold level. The lower levels of antimony and arsenic exposure in animals of the 4th experimental group during this period did not reach the threshold of subacute nephrotoxic effect.

On the 90th day of the subchronic test, animals of the 2nd and 4th experimental groups exposed to a binary mixture of antimony and arsenic in medium doses, respectively, showed a significant decrease in urine osmolarity and excretion of osmotically active substances. In addition, with increased exposure to antimony and arsenic in the 1st experimental group, there was a significant increase in sodium excretion, which indicated an increase in the number of kidney functions involved in the toxic process. The absence of significant differences between the values of the studied parameters in the 3rd experimental and control groups during this period of examination is probably explained by the development of the compensation phase of chronic intoxication in experimental rats. The revealed statistically significant differences in changes in urine osmolarity values in the 4th experimental group on the 90th day of the subchronic test from the parallel control are a generally accepted sign of the minimum effective (threshold) level, that may be a consequence of accumulation of toxicants in kidney tissues or damage to the nephron during excretion. This effect can also be explained by the phenomenon of functional accumulation under conditions of a more than additive effect of antimony and arsenic on kidney function when they enter the body of rats of the 4th experimental group in subthreshold doses.

The totality of actual changes in renal function was not detected at rest on an empty stomach, but was diagnosed under conditions of a water load test (3% of body weight), when it was necessary to activate reserve mechanisms for regulating the water-salt balance.

Thus, the study of rat kidney function as a marker of the body's response to the combined toxic effects of arsenic and antimony, polluting water in mining areas, in a subchronic test provided new information about the nature and dynamics of the nephrotoxic effect. A quantitative assessment of individual indicators of the complex renal response to antimony and arsenic exposure revealed the formation of typical dose-effect relationships.

The nonlinear nature of the dose-effect dependences in quantifying the nephrotoxic effect on the 40th and 90th days of exposure reflects the regular development of non-specific adaptive and compensatory processes. From the standpoint of pathogenetic assessment, the diagnosed effect is the result of the combined toxic effects of antimony and arsenic and consists in disorders of the renal excretory function, which are clearly manifested during water load test.

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