Arsenic Trioxide: Estimation of Health Risks on the Basis of Toxicokinetics Indices

Ms. Manana Juruli[1)] and Dr. Givi Katsitadze[2)]

[1)] N. Makhviladze Institute of Labor Medicine and Ecology,

[2)] Hospital of Iv.Javakhishvili Tbilisi State University,

60 D.Agmashenebeli Ave

0102, Tbilisi, Georgia

mjuruli@myoffice.ge / ekotox@myoffice.ge

ABSTRACT

This work was undertaken for the purpose of studying the toxicokinetics of arsenic trioxide and of attempting to evaluate the toxicity of agent when administered enterally to rats. It has been shown that the arsenic concentration in blood eliminated with a three-phase pattern. Arsenic has long half-times and the tendency to accumulate in the body. Excretion rate fell with eliminating blood concentration. Kinetic parameters, determined in this study might be helpful for management of acute poisoning caused by arsenic compounds.

Keywords: *Arsenic trioxide, experimental study, rats, oral doses, single administration, toxicokinetics, biomonitoring, diagnosis, treatment, prognosis, poisoning*

1.0 INTRODUCTION

Widespread contamination of the environment by toxic chemicals poses ecologic threats and some specific health hazards. The resulting clinical picture may be that of acute, subacute or chronic poisoning. Arsenic (As) has been considered a potent poison since antiquity. Inorganic arsenic, in trivalent state, is a strong protoplasmic poison with a long tradition of use as a homicidal agent and often applied for military purposes to kill and injure people [1]. Large doses of inorganic arsenic lead to neurologic, muscular, renal and gastrointestinal manifestation which may be responsible for a fatal outcome [2]. Prolonged administration can cause hepatocelular carcinoma [3] in experimental animals, angiosarcoma of the liver [4] and carcinoma of skin and lung [5]. The US EPA has classified arsenic as a known human carcinogen (6). To evaluate of health risks and develop strategy for diagnoses and treatment of poisoning, it is a very important to know the fate of chemical in the body, and especially its kinetic properties. A great volume of material has been presented on the toxicodynamics and toxicokinetics of arsenic. But little attention appears to have been given to toxicokinetics of arsenic after single administration of different doses.

Aim of this study is to investigate the toxicokinetics of arsenic trioxide when administered enterally to rats and to evaluate the health risk of agent on the basis of kinetic indices.

2.0 METHODS

Male rats weighing 250 to 300 g were used for the study. The experimental animals were divided into three groups. Rats of group (I) received 100 mg/kg oral single dose of arsenic trioxide. Animals of group (II) received 30 mg/kg (Lim_{ac}), and animals of group (III) 3 mg/kg (0,1 Lim_{ac}). Blood was collected on

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heparin.The amount of As in blood was determined before and at 15 min, 2,24 hours, 2,3,5,10, 20 days after its compilation until it had completely disappeared from blood.

The arsenic content determined by means of the spectrophotometer method with silver dyethildithiocarbamate [7]. Dry ashing procedure with the presence of magnesium oxide (MgO) and magnesium nitrate ($MgNO_3$) was applied for mineralization of biosubtrates [8, 9].

Toxicokintics of arsenic described by exponential equations. The graphs of concentration-time curves were drown using log-linear graph paper; the slope was calculated by taking the logs of the concentration terms and dividing by the time. Elimination half-life were calculated assuming described compartment model ($T_{0,5}$ = 0,693/k) [10, 11].

3.0 RESULTS

The results of the study are given in Table 1. It is evident from this table that after oral administration of 100 mg/kg to rats, arsenic was detected in the blood at once after 15 minute of administration. Then its concentration increased and reach the maximum level (101,56 ± 3,05 mkg/ ml) after 2 days. Since that concentration of arsenic declined during 70 days.

In the case of treshold and sub-treshold doses (30 mg/kg and 3 mg/kg), the maximum level of arsenic was reached after 24 hours (67, 70 ± 1,13 mkg/ml and 17,12 ± 0,35 respectively). Completely arsenic eliminated from blood at the treshold level for 20 days, and at the sub-treshold level for 7 days.

Table 1. Blood arsenic concentration in rats after oral single doses (3, 30 and 100mg/kg) of arsenic trioxide

TIME	DOSE, mg/kg		
	100	30	3
min 15	4,05 ± 0,6	not determined	not determined
hours 1	5,58 ± 0,21	1,68 ± 0,14	not determined
24	77,88 ± 0,88	67,70 ±1,13	17,12 ± 0,35
days 2	101,56 ± 1,48	51,85 ± 1,55	7,06 ± 0,24
3	-	37,38 ± 1,31	4,22 ± 0,25
5	50,68 ± 0,5	22,22 ±1,38	2,57 ±0,13
10	27,83 ± 0,99	8,33 ± 1,16	not determined
20	8,33 ± 0,92	not determined	not determined
30	4,97 ± 0,69	not determined	not determined
60	1,56 ± 0,09	-	-
70	1,13 ± 0,06	-	-

The investigation of the kinetics of the removing the arsenic from blood has allowed to describe this process in the manner of three-phase exponential equations (See table 2). First phase reflects the fast elimination of arsenic, the second - slow, and the third – very slow.

Table 2. Exponential equations showing arsenic blood elimination

Group	Single oral dose of As_2O_3, mg/kg	Exponential equations
I	100	$C_{t(100\%)} = 60e^{-0,29t} + 29e^{-0,13t} + 11e^{-0,004t}$
II	30	$C_{t(100\%)} = 63e^{-0,33t} + 28e^{-0,19t} + 9e^{-0,06t}$
III	3	$C_{t(100\%)} = 46e^{-0,77t} + 28e^{-0,30t} + 26e^{-0,24t}$

Moreover, velocity of the removing the poison interconnected with dose of arsenic trioxide. The dependency between the single oral doses of arsenic trioxide and half life ($T_{0,5}$) is submitted in table 3. From table follows that lengthening of $T_{0,5}$ is detected with dose of 30 mg/kg.

Table 3. Half life ($T_{0,5}$) and the single oral doses of arsenic trioxide

Group	Single oral dose of As_2O_3, mg/kg	Half life ($T_{0,5}$), days		
		T_1	T_2	T_3
I	100	2,4	5,4	17,2
II	30	2,1	3,6	10,9
III	3	0,9	2,3	3,0

4.0 CONCLUSION

It has been shown that all doses of arsenic trioxide characterized by different toxicokinetics parameters. Arsenic has long half-lifes and the tendency to accumulate in the body. Excretion rate fell with eliminating blood concentration. The present study confirms the ability of toxicokinetic models for ameliorative study of various toxic substances. Used tests are specific and helpful in reducing to a minimum probability of wrong conclusions. Therefore, the above toxicokinetics indices can be used as biological monitoring tools for evaluation of the health risks caused by arsenic compounds.

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