Comparative Study of the Biochemical Behavior of some Highly Toxic Minerals on Selenosis in Rats

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Research

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Abstract

Objective: An investigation of the potential influences of As, Hg, Tl and Pb on Se metabolism, which can suggest new drugs to cope the poisonousness of Se.

Methods: Chronic cases were carried out with the nursing of rats with a purified diet of water-soluble vitamin mix, fat-soluble vitamin mix, saccharides, oil, and salts. One week after the basic diet, the rats taken Se have received diets containing 10 ppm of the element as sodium selenite or selenate added in the salts.

Result: As, Hg, and Tl were repressed the volatized Se excreted from the lungs. As has assisted the biliary excretion of Se and inhibited the chronic selenosis. Tl has increased the retention of Se in the liver and kidney, but, had no chronic effect on the amount of Se deposited in all the studied tissues. Similarly, Hg has increased the retention of Se but in the spleen and carcass of rats indicating to the high Se concentration in blood. Hg and Tl have inhibited the Se in urine.

Conclusion: No effects of the doses rich in As, Hg, and Tl on the Se excretion in fecal. Even though, we suggest As as a possible medication to chronic selenosis.

Introduction

Recently, many countries have posed several legislations [1] and slated very specific strategies [2] in pharmaceutical industry that serve health challenge [3]. However, these created new modifying rules and regulations should control the added ingredients to the drugs including minerals and radioactive materials but in innocuous quantities [1, 2]. These supplemented constituents to the pharmaceutical products should be analyzed in reliable analytical procedures [4] which must satisfy the international pharmacological standards [2].

Among such trials, Hamid et al. [5] has stimulated much research concerning the metabolism of toxic elements as selenium. However, this element is mostly existed in biological medium as selenite (SeO$_3^{-2}$) and selenate (SeO$_4^{-2}$).

Selenite is called as gypsum flower, desert rose, satin spar, and satin spar are four assortments of mineral crystals of gypsum. Those four kinds of gypsum can be assembled together and termed selenite [6]. The selenite anion is a Se oxoanion of a formula SeO$_3^{-2}$. A selenite is a compound of this ion. Under weak acidic conditions, hydrogenselenite ion, HSeO$_3^{-}$, is formed; however, in higher acid cases, selenous acid H$_2$SeO$_3$, occurs. It is more required in minute quantities for the proper growth, development, and physiology of an organism [7]. SeO$_3^{-2}$ exacerbates hepatic insulin resistance in mouse model of type II diabetes through oxidative stress-mediated JNK pathway [8]. In A549 cancer cells, the discerning increment of SOD1 content is accompanied with SeO$_3^{-2}$ generation of superoxide radical anions and this boosts apoptosis and Se-Cu linkage [7].
Selenate is a sturdy dibasic acid with molecular formula \((\text{H}_2\text{SeO}_4)\), so it is an acid form of inorganic salts of dihydrogen selenium tetraoxide. It is toxic by dust ingestion, inhalation or skin contact. Selenate is naturally occurring or synthetic substances that inhibit or retard oxidation reactions. They counteract the damaging effects of oxidation in animal tissues [6].

By hand, several metabolic interrelationships among minerals and Se are instituted [9, 10]. As represses Se toxicity [11, 12] and diminishes Se retention in mice’ livers [13]. This advantageous trait of As is owing to the augmented clearance of Se from liver into bile [14].

Cd inhibits Se detoxification and forms volatile methylated Se compounds, so results in increasing Se retained in liver [15–17]. However, Cd in rats which causes testis injury can be protected by Se [17–19].

Novel studies show that Se can protect against Hg and Tl toxification [20–23]. The aim of the current study was to compare the influences of As, Hg, Tl, and Pb on Se metabolism. It was concluded that As, Hg, and Tl all repressed the pulmonary excreted amount of Se volatilized compounds, but that As alone was capable to improve the excretion of Se in bile. As was also the only cooperating tested element that reduced the chronic Se poisoning effects.

**Methods**

*Acute studies.* Nursling male of Holtzman rats (in small bowels, one contained significantly lower concentrations of adenosine – 3',5' - cyclic monophosphate than all the others) (Photo 1) was nourished a stock diet [23] for 2–3 weeks and their pulmonary excretions of exhausted Se compounds were assessed.

The animals were shot subcutaneously in one hind flank with the appropriate test element in physiological saline and then 10 min later in the opposite hind flank with 2 mg Se per kg as sodium selenite (\(\text{Na}_2\text{SeO}_3\)) containing approximately 1 microcurie (\(\mu\text{Ci}\)) of \(\text{H}_2^{75}\text{SeO}_3\) (Preliminary observation: a formation of dimethylselenide (\(\text{CH}_2\text{Se}\)) and dimethyldiselenide (\(\text{CH}_3\) \(\text{Se}_2\)) in the breath of the rats). For capturing the exhausted Se, the animals were left 12 hours in all-glass metabolism cages furnished with sintered-glass scrubbers containing 8N HNO\(_3\). The rats were sacrificed, and the tissues were isolated for direct measurement of radioactivity in a well-type scintillation counter (Perkin Elmer Tri-Carb). Data are expressed as percentage of the dose of labeled selenium injected.

In newborn Holtzman male rats nursed a routine diet, Se excretion from the bile has been investigated. The bile ducts have been cannulated as described in many works [24–26]. In one flank, about 0.5 \(\mu\text{Ci}\) of radioactive Se in physiological saline was subcutaneously injected, and the participating element was given in the opposite flank.

Dose and timing schedules are registered in Tables I-3. Where required, radioselenate was made by a repetitive digestion of radioselenite with conc. HNO\(_3\) [27, 28]. Bile was collected for 1 hour and the radioactivity was detected in a well-type scintillation counter. Data are expressed as percentage of the dose of labeled selenium injected.
Chronic studies. Neonatal masculine Holtzman rats were nourished a purified diet which included the following components in g/kg: sucrose (C\(_{12}H_{22}O_{11}\)), 710; casein (C\(_{38}H_{57}N_{9}O_{9}\)), 200; corn oil (calories, total fat were 122 and 21%, respectively) 50; salts [29], 35; water-soluble vitamin mix, 2; fat-soluble vitamin mix, 2; and choline chloride (CH\(_3\)\(_3\)NCH\(_2\)CH\(_2\)OH)Cl, 1. The water-soluble vitamin mix contained, in mg/g: myo-inositol (C\(_6H_{12}O_6\)), 100; nicotinic acid (vitamin B3 (VB3), C\(_6H_5NO_2\)), 11; calcium pantothenate (Ca salt of water-soluble VB5, C\(_{18}H_{32}CaN_2O_{10}\)), 6; riboflavin (VB2, C\(_{17}H_{20}N_4O_6\)), 2; pyridoxine. HCl (4-methanol form of VB6, C\(_8H_{12}ClN_3O_3\)), 1; thiamine. HCl (VB1, C\(_{12}H_{18}Cl_2N_4OS\)), 1; folic acid (VB9, C\(_{19}H_{19}N_7O_6\)), 0.1; \(d\)-biotin (VB7, C\(_{19}H_{19}N_7O_6\)), 0.1; VB12, 0.005; sucrose (C\(_{12}H_{22}O_{11}\)), 878.8. The fat-soluble vitamin mixture supplied, per kg of diet, 3000 IU of crystalline VA, 2000 IU of VD3, 90 mg of dl-\(\alpha\)-tocopherol (C\(_{31}H_{52}O_3\)), and 150 µg of menadione (C\(_6H_4(CO)_2C_2H(CH_3)\)). The rats were distributed into sets of analogous mean weights and launched their investigational diets after one week on basal food regime.

The rats fed selenium received diets containing 10 ppm of the element as Na\(_2\)SeO\(_3\) or Na\(_2\)SeO\(_4\) added in the salts. So that, the tested elements were participated by means of their soluble salts at a level of 10 ppm in the potable water to examine their impacts on Se metabolism and toxification. The weights were logged twice each 7-days. The living rats were sacrificed and checked for gross pathological lesions. Samples of tissues were frozen and saved for selenium analysis by calorimetry [30–33].

Results

Acute studies

30% of the dosage was exhaled as Se volatilized shape in 12 hours of injecting the control animals with 2 mg Se/kg as SeO\(_3\)\(^{–2}\) and saline (Table 1). The quantity of the volatilized Se was diminished to 5.4% of dosage when the rats were administered 4 mg As/kg as arsenite (AsO\(_2\)\(^{–}\)). Even the animals needed higher dosages, but we registered a pulmonary Se excretion inhibition when Hg or Tl was administered. High dosages of Pb (48 mg/kg) did not show any effect on the Se circulation or volatilization. However, the noticeable reduction of the Se volatilized shape during As and Hg treatment was followed with high levels of Se in the kidney and carcass. Treatment with Tl had retained higher amounts of Se in the kidney and liver. Possibly due to the Se increasing concentrations in the gastrointestinal innards, high quantities of Se in the carcass were enrolled when As has been taken [34]. In addition, probably due to the extremely high concentration of Se in blood, the retention of this element in carcass has been noticed during Hg intake. This is not just the interesting notice with Hg administration in rats, nevertheless, we also observed a large amount of Se retained in spleen.
Table 1
Effect of $\text{AsO}_2^-$ and the collaborated chemical elements on $\text{SeO}_3^{2-}$ metabolism by rats.

| Chemical form and dosage of test elements$^b$ (mg/kg) | Proportion of the dose of selenium (%)$^a$ | Volatile compounds | Liver | Kidney | Carcass$^c$ | Spleen | Blood, ml | Feces | Urine |
|--------------------------------------------------|-------------------------------------------|--------------------|-------|--------|------------|--------|-----------|-------|-------|
| None                                             |                                           |                    | 30.6 ± 3.72 | 11.3 ± 0.02 | 1.90 ± 0.11 | 20.2 ± 1.07 | 0.20 ± 0.05 | 0.80 ± 0.16 | 1.10 ± 0.54 | 14.7 ± 2.38 |
| $\text{NaAsO}_2^-$-4                             |                                           |                    | 5.40 ± 0.74  | 8.65 ± 0.01  | 5.02 ± 0.29  | 42.8 ± 1.70 | 0.10 ± 0.05  | 0.40 ± 0.02  | 0.40 ± 0.32  | 16.0 ± 0.97   |
| $\text{HgCl}_2$-12                               |                                           |                    | 8.70 ± 2.11  | 15.8 ± 0.84  | 4.23 ± 0.27  | 37.4 ± 0.60 | 1.80 ± 0.11  | 1.70 ± 0.20  | 0.50 ± 0.20  | 7.80 ± 1.60   |
| $\text{TlAc}$-12                                 |                                           |                    | 5.90 ± 1.27  | 37.5 ± 6.20  | 9.83 ± 0.52  | 17.9 ± 1.20 | 0.30 ± 0.00  | 0.42 ± 0.00  | 0.90 ± 0.21  | 6.33 ± 0.50   |
| $\text{Pb(Ac)}_2$-48                             |                                           |                    | 32.6 ± 2.40  | 13.7 ± 2.65  | 2.17 ± 0.36  | 21.3 ± 1.40 | 0.34 ± 0.10  | 1.15 ± 0.40  | 0.92 ± 0.50  | 13.9 ± 0.60   |

$^a$ Distribution of radioactivity 12 hours after subcutaneous injection of 2 mg of Se per kilogram body weight containing approximately 1 µCi $^{75}\text{Se}$ as $\text{H}_2^{75}\text{SeO}_3$; mean of four animals ± standard error; weight range of animals 119–189 g.

$^b$ Before injecting with Se by 10 min, the rat has been injected with saline solution or the test element subcutaneously.

$^c$ Includes gastrointestinal contents.

No treatment of the groups in any of these short-interim testing was affected Se fecal excretion, but the depressing properties of TI and Hg on Se in urine were recorded. Similar to the Experiment A presented in Table 2, in another study [24], As has promoted Se bile excretion. Animals receiving only selenium excreted about 1% of the dose in the bile in 1 hour whereas animals receiving both arsenic and selenium excreted over 20% of the dose of selenium in the same time interval. Under similar tentative conditions, trials of using Hg, TI, or Pb were failed to initiate Se excretion from the bile.
Table 2
Effect of AsO$_2^-$ and heavy metals (i.e. Hg, Tl, Pb) on Se excretion in bile.

| Chemical form and dosage (mg element/kg) | Proportion of the dose of selenium (%)$^d$ |
|----------------------------------------|------------------------------------------|
| Selenium                                | Test element                             | Bile          | Liver          |
| Experiment A$^e$                        |                                          |               |               |
| Na$_2$SeO$_3$-0.5                       | None                                     | 1.18 ± 0.20   | 28.6 ± 1.01   |
| Na$_2$SeO$_3$-0.5                       | NaAsO$_2$-1                              | 21.2 ± 4.47   | 10.6 ± 1.73   |
| Na$_2$SeO$_3$-0.5                       | HgCl$_2$-1                               | 1.50 ± 0.32   | 28.8 ± 1.51   |
| Na$_2$SeO$_3$-0.5                       | TlAc-1                                   | 0.90 ± 0.25   | 29.3 ± 2.96   |
| Na$_2$SeO$_3$-0.5                       | Pb(Ac)$_2$-l                             | 1.08 ± 0.11   | 28.9 ± 0.74   |
| Na$_2$SeO$_4$-0.5                       | None                                     | 0.90 ± 0.13   | 22.0 ± 2.57   |
| Na$_2$SeO$_4$-0.5                       | NaAsO$_2$-1                              | 3.90 ± 3.69   | 8.10 ± 1.32   |
| Na$_2$SeO$_4$-0.5                       | TlAc-1                                   | 0.90 ± 0.21   | 19.7 ± 2.08   |
| Experiment B$^f$                        |                                          |               |               |
| Na$_2$SeO$_3$-2.4                       | None                                     | 0.34 ± 0.00   | 15.0 ± 0.50   |
| Na$_2$SeO$_3$-2.4                       | HgCl$_2$-4                               | 0.35 ± 0.00   | 15.6 ± 0.80   |
| Experiment C$^g$                        |                                          |               |               |
| Na$_2$SeO$_3$-4.2                       | None                                     | 0.17 ± 0.00   | 10.2 ± 0.60   |
| Na$_2$SeO$_3$-4.2                       | TlAc-30                                  | 0.19 ± 0.01   | 27.4 ± 0.70   |
| Na$_2$SeO$_4$-4.2                       | None                                     | 0.33 ± 0.00   | 10.3 ± 0.30   |
| Na$_2$SeO$_4$-4.2                       | TlAc-30                                  | 0.23 ± 0.50   | 16.5 ± 1.80   |

$^d$ Distribution of radioactivity 1 hour after subcutaneous injection of stated dose of selenium containing approximately 0.5 µCi $^{75}$Se as H$_2$$^{75}$SeO$_3$ or H$_2$$^{75}$SeO$_4$; weight range of animals 344–403 g; mean of three or four animals ± standard error.

$^e$ Se injection followed by 10 min the saline or the specified test element injection subcutaneously.

$^f$ Se injection after 1 hour of injection subcutaneously with the saline or the specified dose of Hg.

$^g$ Se injection after 2 hrs of injection subcutaneously with the saline or the specified dose of Tl.
Yet, As may possess diverse impacts on Se metabolism depending on the time interval between injections, valance state, and dose of the elements [35, 36]. Similar reports to the current experiments had demonstrated an antagonism effect of Se against Tl and Hg [35–38]. Even though, according to the Experiments B & C in Table 2 and under the prespecified conditions, Tl and Hg have not exhibited any effect on Se excretion from the bile. Likewise, that was also right once Tl was experienced along with Se introduction as selenate (SeO$_4^{2−}$) in lieu of SeO$_3^{2−}$.

**Chronic studies**

Conferring to Experiment A in Table 3, As was the one tested element that shielded rats against chronic selenosis [39] as ruled by 3-unlike measures: reduced liver damage, reduced Se retention in diverse tissues, and high mass gains. Under parallel conditions, compared to the rats which did not fed Se, these animals that received Se + As have exercised no substantial growth-promoting effect even they showed growing mass gain (the mass gain of control and As treated animals was 235 ± 9.80 and 249 ± 15.5 g, respectively, P > 0.3). This cluster of rats which supplemented Se + As exhibited quite pretty normal on gross checkup, even just a few showed a little grainy appearance. However, an extreme plain form of liver injury was observed uniform with seleniferous control. Hg administration to the animals has associated with mass gain in analogy to the As set, however, they conveyed ascites fluid. Besides, the survival was lowermost archived in this set and the liver damage has been largely dominant in the control set who acknowledged Se alone. Thallium did not improve weight gains although in this group there was a slightly favorable effect against liver damage due to selenium. Giving the results of Experiment B that presented in Table 3 and in equivalent to the previous tests, Tl and Se provided as SeO$_4^{2−}$ in lieu of SeO$_3^{2−}$, has shaped parallel outcomes. As component critically depressed the quantity of Se reserved in the tissues of animal nourished enduring contents of Se, despite the rats possibly assimilated extra meal comprising this element, as evinced by their larger mass gains. Hg was virtually not active as As, in spite of, the first element leaned to decline to a certain degree the Se retained in liver and kidney. Tl did not demonstrate any effect on the precipitated Se content in the tissues of the animal administered Se as SeO$_3^{2−}$. Moreover, the latter testing element (Tl) was fairly diminished the quantity of the Se compounds retained in livers of SeO$_4^{2−}$-fed rats. However, more notably, Tl resulted an increase in the content of Se observed in kidney.
Table 3
Effect of $\text{AsO}_2^-$ and heavy metals in chronic selenosis.

| Salt in drinking water<sup>h</sup> | Weight gain (g) | Survival | Gross liver damage | Se content (µg/g wet weight) |
|-----------------------------------|----------------|----------|--------------------|-----------------------------|
|                                   |                |          |                    | Liver                       | Kidney                      |
| Experiment A<sup>i</sup>           |                |          |                    |                             |
| None                              | 68.9 ± 8.91    | 9/10     | Severe             | 7.64 ± 2.10                 | 36.8 ± 2.76                 |
| $\text{NaAsO}_2$                  | 116 ± 16.3     | 8/10     | Mild               | 2.72 ± 0.20                 | 11.5 ± 2.30                 |
| $\text{HgCl}_2$                   | 105 ± 34.3     | 4/7      | Severe             | 6.60 ± 0.90                 | 24.3 ± 4.82                 |
| $\text{TlAc}$                     | 70.0 ± 8.25    | 6/7      | Moderately severe  | 7.48 ± 0.60                 | 33.3 ± 6.50                 |
| Experiment B<sup>j</sup>           |                |          |                    |                             |
| None                              | 75.0 ± 8.50    | 6/7      | Severe             | 22.1 ± 5.80                 | 42.5 ± 6.61                 |
| $\text{TlAc}$                     | 72.0 ± 11.9    | 6/7      | Moderately severe  | 14.3 ± 1.70                 | 104.4 ± 5.30                |

<sup>h</sup> Add at level of 10 ppm of the test element.

<sup>i</sup> After 7 weeks on a diet containing 10 ppm Se as $\text{SeO}_3^-$; mean ± standard error.

<sup>j</sup> After 7 weeks on a diet containing 10 ppm Se as $\text{SeO}_4^-$.

**Discussion**

The current findings establish an exceptional aptitude of As to develop the excretion of Se bile and lessen Se toxication. The chronically selenized animals taken As showed a reduction in the Se retained in livers, makes it look as if appear that the valuable factor of As in chronic selenium poisoning is probably related to the increased Se excretion into the bile of As-handled rats. The later action of As performance on biliary Se is left over for further deep investigations to explain this important mechanism.

Ostensibly, Se pulmonary excretive reduction per se did not entail adequate conditions for enhancing Se excretion in bile, probably for a reason that As, Tl, and Hg can impede the biosynthesis of Se volatile compounds. However, As is the sole among the other tested elements that has enthused the excretion of Se in bile. Likewise, the augmented quantity of Se in the bile of As-handled animals has not seemed to be associated to a wide-ranging infiltration of As on the active thiol functional groups of structural proteins or enzymes [40–43] attributing to the only fact that Pb, Tl, and Hg all attack and strongly react with thiol groups (sulfhydryl, $\sim$SH) as well [44] and might be expected to mimic the effect of arsenic where this the lone factor involved.
The probability of constructing specific selenoarsenic conjugates as purifying agents excreted into the bile is being deliberated beforehand [11]. Nevertheless, the present biochemical fractionation investigations that propose an incidence of numerous diverse forms of biliary Se, lean towards rejecting this supposition.

**Conclusion And Recommendations**

**Conclusion**

The metabolism of Se is reliant on the valency state and the dose amount of the elements, in addition to the interval period among shoots. In addition, we refer clearly to the antagonism property including biliary excretion of Se against Hg and Tl. As compounds have successfully proved themselves as a medication of liver damage, which can be suggested as supplemented ingredients in releasing Se from various tissues.

**Recommendations**

More studies are needed to investigate the mechanism of the valuable arsenic performance in treating biliary selenium.

**Declarations**

**Conflict of Interest**

We have no conflicts of interest.

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**Availability of data and materials**

Data is available upon request.

**Ethics approval and consent to participate**

Concerning ethical issues, the proposed study was approved by the USEPA and ethics committee.

**Consent for publication**

Not applicable. This study does not contain any individual or personal data.

**Competing interests**
The author declares no competing interests.

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**Figures**

![Figure 1](image-url)

**Figure 1**

Newborn Holtzman rat males.