Research Paper

Combined administration of taurine and monoisoamyl DMSA protects arsenic induced oxidative injury in rats

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Abbreviations: δ-ALAD, delta-aminolevulinic acid dehydratase; AAS, atomic absorption spectrophotometer; As, arsenic; DMSA, meso 2,3-dimercaptosuccinic acid; GSH, reduced glutathione; GSSG, oxidized glutathione; SOD, superoxide dismutase; Hb, haemoglobin; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume; MiADMSA, monoisoamyl 2,3-dimercaptosuccinic acid; PCV, packed cell volume; RBC, red blood cell; ROS, reactive oxygen species; TBARS, thiobarbituric acid reactive substances; WBC, white blood corpuscles; ZPP, zinc protoporphyrin

Key words: arsenic toxicity, oxidative stress, taurine, chelation

Arsenic is a naturally occurring element that is ubiquitously present in the environment. High concentration of naturally occurring arsenic in drinking water is a major health problem in different parts of the world. Despite arsenic being a health hazard and a well documented carcinogen, no safe, effective and specific preventative or therapeutic measures are available. Among various recent strategies adopted, administration of an antioxidant has been reported to be the most effective. The present study was designed to evaluate the therapeutic efficacy of monoisoamyl dimercapto-succinic acid (MiADMSA), administered either individually or in combination with taurine post chronic arsenic exposure in rats. Arsenic exposed male rats (25 ppm, sodium arsenite in drinking water for 24 weeks) were treated with taurine (100 mg/kg, i.p., once daily), monoisoamyl dimercaptosuccinic acid (MiADMSA) (50 mg/kg, oral, once daily) either individually or in combination for 5 consecutive days. Biochemical variables indicative of oxidative stress along-with arsenic concentration in blood, liver and kidney were measured. Arsenic exposure significantly reduced blood δ-aminolevulinic acid dehydratase (ALAD) activity, a key enzyme involved in the heme biosynthesis and enhanced zinc protoporphyrin (ZPP) level. Clinical hematological variables like white blood cells (WBC), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) showed significant decrease with a significant elevation in platelet (PLT) count. These changes were accompanied by significant decrease in superoxide dismutase (SOD) activity and increased catalase activity. Arsenic exposure caused a significant decrease in hepatic and renal glutathione (GSH) level and an increase in oxidized glutathione (GSSG). These biochemical changes were correlated with an increased uptake of arsenic in blood, liver and kidney. Administration of taurine significantly reduced hepatic oxidative stress however co-administration of a higher dose of taurine (100 mg/kg) and MiADMSA provided more pronounced effects in improving the antioxidant status of liver and kidney and reducing body arsenic burden compared to the individual treatment of MiADMSA or taurine. The results suggest that in order to achieve better effects of chelation therapy, co-administration of taurine with MiADMSA might be preferred.

Introduction

The drinking water containing arsenic more than 10 µg/L is harmful to the body.¹ The main source of this arsenic contamination is the shallow tube wells, having more than 500 µg/L of arsenic.² Heavy reliance of agriculture on new water wells has lead to extensive chronic arsenic poisoning in certain parts of countries like Bangladesh, India (West Bengal) and China (Inner Mongolia).³⁴ In addition to the natural sources of arsenic contamination in drinking water, use of arsenic-containing herbicides, insecticides, rodenticides, preservatives and by-products of fossil fuels are enough to challenge the aquatic environment as well as humankind.⁵ Arsenic induced oxidative stress in blood and other soft tissues has been postulated to be one of the possible mechanisms of arsenic induced toxic effects.⁶⁻⁹ Disruption of pro-oxidant/antioxidant balance might lead to tissue injury. An increased arsenic concentration has been shown to be accompanied by increased lipid per-oxidation in animal tissues.¹⁰ Exposure to sodium arsenite has been reported to significantly decrease glutathione (GSH) level, superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase activity.⁹ Maiti and Chatterjee¹¹ reported that liver and kidneys have different adaptive cellular protective mechanism against arsenic exposure.

The current approved clinical intervention against arsenic toxicity is to give chelating agents which form an insoluble complex with arsenic and remove it from the burdened tissues. Most of these chelating agents however, suffer from serious side effects.¹²¹³ Clinical reliance on meso 2,3-dimercaptosuccinic acid (DMSA), an orally administered chelator, has expanded greatly during the last few years.
Taurine is a strong acid that makes it completely zwitterionic over the physiological pH range. Taurine is known to maintain calcium homeostasis, osmoregulation, removal of hypochlorous acid, and stabilizing the membranes. It’s potential as a chelating agent against lead poisoning has been reported by us.

We concluded that DMSA being relatively efficient and non-toxic chelator, MiADMSA should also be of greater interest particularly as a potential drug for chelation therapy in arsenic poisoning. One of the major drawbacks of chelation therapy is related to redistribution of toxic metals to other tissues, especially to the brain. No such redistribution was observed with MiADMSA administration. Mehta and Flora reported that administration of MiADMSA may lead to copper loss and also mild hepatotoxicity. It indicates greater complexing potential of DMSA monoester compared to DMSA. The depletion of essential metals does not necessarily result in the pronounced excretion of the metal in the urine. A number of previous reports have indicated an increased uptake of zinc and copper with no alteration in urinary copper and zinc following DMSA administration.

It has also been reported that chelator is relatively safe during late gestation and it does not cause any major alteration in the mothers and the developing pups. Despite a few drawbacks/side effects associated with MiADMSA, MiADMSA is being considered recently as a future drug of choice owing to its specificity, accessibility to intracellular spaces and the absence of essential metal redistribution.

Moderate toxicity followed by administration of MiADMSA may be reversible after withdrawal of chelating agent.

As mentioned above, arsenic induced oxidative stress is one of the possible mechanisms involved in the pathogenesis of arsenic poisoning. Thus, it is believed that supplementation of an antioxidant during treatment should be one of the important components of an effective arsenic therapy. Some of the antioxidants like n-acetylcysteine (NAC) have been proved to be beneficial both in reducing oxidative stress and arsenic burden. Such dual benefits of these chelators and/or antioxidant support their use in combination. This may support the theory (combination treatment) for a more effective treatment of arsenic poisoned compared to their individual treatment.

Taurine is a naturally occurring antioxidant and a drug used for the treatment of diabetic polyneuropathy (structure shown in Fig. 1). It has a thiol group and found naturally in plants and animals. Taurine is a sulphur containing δ-amino acid found in millimolar concentrations especially in tissues that are excitable, rich in membranes and generates oxidants. The sulfonate group in taurine is a strong acid that makes it completely zwitterionic.
Table 1: Effects of MiADMSA and taurine co-administration on some arsenic sensitive biochemical variables suggestive of altered heme biosynthesis pathway and oxidative stress

|                  | ALAD (nmol/min/ml erythrocytes) | ZPP (µmol ZPP/mol heme) | GSH (mg/ml) |
|------------------|---------------------------------|-------------------------|-------------|
| Normal animals   | 9.86 ± 0.80*                    | 61.0 ± 0.66*            | 5.00 ± 0.33*|
| Arsenic, 25 ppm  | 4.30 ± 0.17†                    | 96.3 ± 6.11†            | 4.38 ± 0.62*|
| Taurine, 100 mg/kg | 4.63 ± 0.17†                  | 93.6 ± 1.45†            | 4.49 ± 0.17*|
| MiADMSA, 50 mg/kg | 5.00 ± 0.10†                   | 79.0 ± 3.00†            | 4.89 ± 0.08*|
| MiADMSA + Taurine, 50 mg/kg | 5.60 ± 0.13†                | 83.3 ± 10.4†            | 4.84 ± 0.07*|
| MiADMSA + Taurine, 100 mg/kg | 8.10 ± 0.70‡                 | 85.2 ± 8.03†            | 5.04 ± 0.03*|

ALAD, δ-aminolevulinic acid dehydratase; ZPP, zinc protoporphyrin; GSH, reduced glutathione; MiADMSA, monoisamyldimercaptosuccinic acid. Values are mean ± SE; n = 5; * Means with matching symbol notations in each column are not significant at 5% level of significance.

Table 2: Effects of MiADMSA and taurine co-administration on some clinical hematological variables

|                  | WBC (10⁶/µl) | RBC (10⁹/µl) | PLT (10⁶/µl) | Hb (g/dl) | HCT (%) |
|------------------|--------------|--------------|--------------|-----------|---------|
| Normal animals   | 7.54 ± 1.76* | 5.0 ± 0.88*  | 782 ± 98*    | 11.6 ± 0.21* | 37 ± 5.3* |
| Arsenic, 25 ppm  | 3.65 ± 0.31† | 6.4 ± 0.25*  | 1203 ± 126†  | 11.9 ± 0.60* | 43 ± 1.6* |
| Taurine, 100 mg/kg | 3.25 ± 0.11† | 7.2 ± 0.29*  | 918 ± 64†    | 13.2 ± 0.36* | 47 ± 1.1* |
| MiADMSA, 50 mg/kg | 2.95 ± 0.61† | 6.7 ± 0.28*  | 1227 ± 75†   | 12.3 ± 0.01* | 45 ± 0.7* |
| MiADMSA + Taurine 50 mg/kg | 3.75 ± 0.83* | 6.7 ± 0.26*  | 1012 ± 191†  | 12.4 ± 0.56* | 45 ± 1.7* |
| MiADMSA + Taurine, 100 mg/kg | 2.82 ± 0.64† | 5.7 ± 1.05*  | 1623 ± 344†  | 12.2 ± 0.34* | 38 ± 5.8* |

WBC, white blood cells; RBC, red blood cells; PLT, platelet; Hb, Hemoglobin; HCT, hematocrit; MiADMSA, monoisamyldimercaptosuccinic acid. Values are mean ± SE; n = 5; * Means with matching symbol notations in each column are not significant at 5% level of significance.

Taurine protects arsenic toxicity

The levels of hepatic GSH, GSSG, and activities of SOD and catalase in animals exposed to arsenic and following treatment with taurine, and MiADMSA, either individually or in combination, are shown in Table 4. Exposure to arsenic significantly reduced hepatic GSH level and increased GSSG concentration while administration of MiADMSA alone significantly reduced arsenic concentration of blood, liver, and kidney. Co-administration of taurine at higher dose (100 mg/kg) with MiADMSA provided the best effects in reducing arsenic concentration from these organs than any other treatments.

Material and Methods

Animals and treatments. Male wistar albino rats weighing approximately 110–120 g were obtained from the Defence Research and Development Establishment (DRDE) animal facility and prior to use, were acclimatized for 7 days 12 h light/dark cycle. The Animal Ethical Committee of the DRDE, Gwalior, India, approved the protocols for the experiments. Rats were divided into two groups of five and twenty five rats each and were treated as below for 24 consecutive weeks,

Group I: Normal animals (Received normal water)
Group II: As (25 ppm, as sodium meta-arsenite, in drinking water)

After 24 weeks of arsenic exposure, animals in Group II were subdivided into 5 groups of five animals each and treated as below for 5 consecutive days:

1. Normal animals
2. Arsenic
3. Taurine
4. MiADMSA
5. MiADMSA + Taurine

Table 2 shows the effect of taurine and MiADMSA either individually or in combination on some selected clinical variables in blood. No significant change in the levels of RBC, Hb and HCT were noted however, WBC level decreased and PLT counts showed significant increase on arsenic exposure. None of the treatments were effective in influencing altered WBC and PLT levels.

Table 3 shows the effect of taurine and MiADMSA either individually or in combination on blood MCV, MCHC and MCH levels in arsenic pre-exposed rats. All the three parameters were significantly decreased on arsenic exposure. Taurine and MiADMSA individually had no effect on these altered clinical variables. Combined administration of a lower dose of taurine (50 mg/kg) with MiADMSA also had no beneficial effects on these variables while the administration of higher dose of taurine (100 mg/kg) with MiADMSA provided significant recovery in MCHC and MCH levels compared to all other treatments.

Figure 3 shows arsenic concentration in blood, liver and kidney of arsenic exposed animals and the ability of taurine, and MiADMSA either alone or in combination to reduce its concentration. Administration of taurine alone had no effect on arsenic levels while administration of MiADMSA alone significantly reduced arsenic concentration of blood, liver, and kidney. Co-administration of taurine at higher dose (100 mg/kg) with MiADMSA provided the best effects in reducing arsenic concentration from these organs than any other treatments.
For blood and tissues metal determination, wet tissue weight and volume of blood was recorded. After digestion with concentrated nitric acid using a microwave digestion system (model MDS-2100, CEM, USA), samples were brought to a constant volume and determination of tissue arsenic contents was performed using a hydride vapor generation system fitted with an atomic absorption spectrophotometer (AAS, Perkin Elmer model AAnalyst 100).

**Discussion**

The present study concludes beneficial role of taurine when administered along with MiADMSA in providing effective reversal of number of arsenic sensitive biochemical variables suggestive of oxidative stress and altered heme biosynthesis pathway. The data provides some interesting observations for suggesting an effective treatment for cases of chronic arsenic poisoning. We understand that extrapolating the animal data to human cases has its limitations particularly for the fact that similar signs and symptoms following chronic arsenic exposure in animal models are difficult. In human cases signs of chronic toxicity appear after long term exposure to a low dose of arsenic and thus we selected comparatively higher dose of arsenic in the present study in animal model for achieving the few similar effects which are seen in human cases. Shila et al. selected 100 ppm dose of arsenite for a 8 weeks exposure in rats in order to evaluate alterations in glutathione level and its response to lipidic acid. For MiADMSA dose protocol, a dose of 50 mg/kg dose through oral route has been reported by us in the previous studies to be ideal to achieve the best therapeutic effects following arsenic

**Table 4  Effects of MiADMSA and taurine co-administration on some biochemical variables suggestive of hepatic oxidative stress**

|               | Catalase (µmole/min/mg protein) | SOD (units/min/mg protein) | GSH (mg/ml) | GSSG (mg/ml) |
|---------------|--------------------------------|---------------------------|-------------|--------------|
| Normal animals| 3.37 ± 0.34*                    | 0.49 ± 0.03*              | 14.4 ± 1.1* | 0.84 ± 0.06* |
| Arsenic, 25 ppm| 7.36 ± 0.62†                   | 0.18 ± 0.03†              | 8.5 ± 1.2†  | 1.97 ± 0.47† |
| Taurine, 100 mg/kg| 2.14 ± 0.51†                  | 0.34 ± 0.03†              | 8.1 ± 1.0†  | 0.50 ± 0.03‡ |
| MiADMSA, 50 mg/kg| 9.19 ± 1.00†                   | 0.26 ± 0.01†              | 9.7 ± 0.8†  | 0.89 ± 0.01* |
| MiADMSA + Taurine 50 mg/kg| 2.98 ± 0.29*                  | 0.35 ± 0.01†              | 9.5 ± 0.9†  | 0.72 ± 0.14* |
| MiADMSA + Taurine, 100 mg/kg| 5.80 ± 0.29‡                  | 0.22 ± 0.01‡              | 11.7 ± 0.6† | 0.77 ± 0.03* |

SOD, superoxide dismutase; GSH, reduced glutathione; GSSG, oxidized glutathione; MiADMSA, monoisoamyl dimercaptosuccinic acid; Values are mean ± SE; n = 5; * †‡Means with matching symbol notations in each column are not significant at 5% level of significance.
Taurine protects arsenic toxicity

Few recent studies reported the superior efficacy of monoisoamyl DMSA (MiADMSA) and mono-n-amyl DMSA in protecting the mice from the lethal effects of arsenic and in reducing body arsenic burden. \(^{38,39}\)

Reactive oxygen species are thought to contribute to the pathogenesis of arsenic toxicity. \(^{40,41}\) Results from the present study also suggest that some of the toxic effects of arsenic could be attributed to the arsenic induced oxidative stress. A significant inhibition of blood ALAD and GSH level and an increase in ZPP level was noted in the present study. It is well known that arsenic affects the haematopoietic system by inhibiting the haem bio-synthesis. The enzyme that is sensitive to the toxic effects of arsenic is probably \(\delta\)-aminolevulinic acid dehydratase (ALAD). ALAD is a sulphydryl-containing enzyme involved in the heme synthesis pathway, and its inhibition can be attributed to the binding of arsenic with sulphydryl groups. Arsenic has got a high affinity for -SH group and it binds with reduced glutathione (GSH). Inhibition of ALAD enzyme by arsenic led to decreased heme synthesis and ultimately anemia. ALAD inactivation may also led to the accumulation of \(\delta\)-aminolevulinic acid that can cause an overproduction of ROS, which in part could explain arsenic induced oxidative stress. \(^{42}\) It has been reported earlier that this significant increase in ALA level might be a contributing factor in the induction of reactive oxygen species (ROS) generation. \(^{43-45}\)

Considerable beneficial effects of taurine particularly at a dose of 100 mg/kg were noted when it was administered alone with MiADMSA on biochemical variables suggestive of oxidative stress. The reversal in the inhibited ALAD activity following treatment with MiADMSA might be attributed to the availability of thiol groups (Fig. 1). Co-administration of MiADMSA with taurine (100 mg/kg) led to a more pronounced recovery in arsenic-induced oxidative injury compared to the individual effects of these drugs. These beneficial effects might be due to (i) depletion of body arsenic burden by MiADMSA and/or (ii) antioxidant action of taurine. \(^{28}\)

Increased catalase activity and decreased SOD activity in liver was also noted following arsenic exposure. Role of taurine in maintaining GSH levels and increasing the status of antioxidant enzymes (SOD, Catalase and GPx) by directly scavenging superoxide radicals and reducing cellular damage caused by free radicals have been reported earlier in lead exposed animals. \(^{46}\) It has been demonstrated that taurine acts as an antioxidant in vivo and in vitro studies. \(^{47}\) The mechanism of the possible antioxidative effects of taurine is unclear, but it has been suggested that the same is related to free radical scavenging activity of taurine. \(^{48}\) The free sulphydryl group in taurine seems to play a significant role as a ROS scavenger. Taurine is neither metabolized nor incorporated into cellular proteins in mammals suggesting ready availability of sulphydryl moiety in cytosol. \(^{27,49}\) Antioxidant potential of taurine has also attributed to its ability to restore metal induced depletion of membrane Na**, K**-ATPase activity. \(^{50}\) Besides the above, mechanism for the antioxidant effect of taurine can also be explained as its direct action to quench and detoxify some reactive intermediate such as hypochlorous acid generated by myeloperoxidase, \(^{50}\) nitric oxide, \(^{51}\) and \(H_2O_2\) \(^{52}\) and indirectly via protecting cells through intercalating into the membrane and stabilizing it. \(^{53}\) The membrane protecting activity of taurine is suggested to be related to its action on permeability to ions and water. \(^{47}\) In this
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study, a direct correlation between arsenic concentration and tissue oxidative injury was noted. Depletion in tissue oxidative stress was accompanied by a decrease in tissue arsenic level. Similar observations were noted where taurine administration protected lead induced oxidative stress in rats. Taurine supplementation also provided significant recovery in depleted SOD activity. SOD, a metalloprotease accomplishes its antioxidant function by protecting the cells against the toxic effects of O2− by catalyzing its dismutation. Provided significant recovery in depleted SOD activity. SOD, a protective effect against thioacetamide hepatotoxicity in rats. and also decreases oxidative stress. Another new and interesting observation in the present study was that taurine at the dose of 100 mg/kg when administered along with MiADMSA provided more pronounced depletion of arsenic concentration in blood, liver and kidneys. This suggests that the antioxidative capacity of taurine becomes most effective only when it is administered along with the thiol chelators or taurine might be facilitating the entry of chelator to the intracellular sites thereby reducing arsenic concentration.

The results thus lead to conclude the beneficial role of taurine when administered along with a thiol chelator but still it remains to be seen if: (i) taurine is a better antioxidant than other available antioxidants in providing significant clinical recovery; (ii) a dose dependent study using a higher dose of taurine need to be attempted; (iii) the exact mechanism of action of taurine needs to be elucidated.

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