Original Article

Effect of vitamin C on oxidative liver injury due to isoniazid in rats

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Abstract  Background: The aim of the present study was to investigate the effect of different doses of vitamin C on oxidative liver injury due to isoniazid (INH) in rats.

Methods: Rats were divided into four subgroups, each containing 10 rats. Group 1 was the control group; group 2, INH 50 mg/kg per day; group 3, INH 50 mg/kg per day + low-dose vitamin C (100 mg/kg per day); group 4, INH 50 mg/kg per day + high-dose vitamin C (1000 mg/kg per day). INH and vitamin C were administered into their stomachs through an oral tube. After 21 days, measurements were made in both serum and homogenized liver tissues. The levels of glutathione (GSH), superoxide dismutase (SOD) and other biochemical variables were measured. Malondialdehyde (MDA), glutathione peroxidase (GSH-px) and vitamin C were measured using commercial kits.

Results: Aspartate amino transferase and alanine aminotransferase in group 2 were higher than those in groups 1, 3 and 4 (P < 0.008 for both). Serum and tissue levels of MDA in group 2 were higher than that in groups 1 and 3 (P < 0.008 for both). There was no difference in the SOD levels between the four groups (P = 0.095). Erythrocyte and tissue GSH in group 2 were higher than that in groups 1 and 3 (P < 0.008 for both). Interestingly, erythrocyte and tissue GSH in group 4 were lower than those in group 1 (P < 0.008 for both). Erythrocyte level of GSH-px in group 2 was higher than that in groups 1 and 3 (P < 0.008 for both).

Conclusions: INH-induced liver injury is associated with oxidative stress, and co-administration of low-dose vitamin C may reduce this damage effectively in a rat model. The antioxidant effect of high-dose vitamin C does not seem more potent compared to the low dose.

Key words  glutathione, hepatotoxicity, isoniazid, oxidative stress, vitamin C.

Isoniazid (INH) is the most preferred drug in both chemoprophylaxis and treatment of tuberculosis.¹,² Daily intake, however, causes moderate elevation in liver enzymes and severe hepatic damage (especially hepatic necrosis) in 3–20% and 1–2% of patients, respectively.¹,² If hepatotoxicity is not recognized early, it may be fatal.³ In humans, the pathogenesis of hepatic toxicity induced by INH is still not clearly known. Most previous studies conducted with rats and humans have shown that hydrazine plays the main role in INH hepatotoxicity, and there are some similarities between INH hepatotoxicity generated in the animal models and that observed in humans.³⁻⁵ Despite the fact that it has been known for 30 years that toxicity occurs in patients treated with INH and that some metabolites play a role in such toxicity, the mechanism by which hepatic damage develops is not still clearly understood.⁵ Recent experimental studies have demonstrated that oxidative stress is one of the mechanisms responsible for INH-induced hepatic injury. Oxidative stress results from an imbalance between oxidants and antioxidants in favor of the oxidants.⁶,⁶ Free oxygen radicals may lead to oxidative damage by lipid peroxidation. One of the aldehyde compounds generated from lipid peroxidation, malondialdehyde (MDA) can be used to evaluate this damage.¹ Aerobic organisms have evolved intricate and interrelated processes for protection against the effects of free radicals and derived toxic species, including both enzymatic and non-enzymatic defenses. Enzymatic mechanisms include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-px). Non-enzymatic mechanisms contain glutathione (GSH), which is the most important cellular antioxidant. The decrease of GSH, SOD, CAT and GSH-px levels and the increase of MDA level are closely related to oxidative stress, and the normalization of those levels by drugs or chemicals is very important in the attenuation of oxidative tissue damage.⁶,⁷ Vitamin C (ascorbic acid) is a strong antioxidant vitamin that is formed during cellular metabolism and which destroys toxic free radicals and other reactive oxygen species (ROS).⁷ Combining INH with an antioxidant substance may reduce the liver damage induced by INH. Ascorbic acid (AA) can easily react with superoxide radical, hydrogen peroxide (H₂O₂) and the ‘singlet’ oxygen, neutralizing them. It clears up the radicals that initiate lipid peroxidation, protecting cell membranes from oxidant damage.

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damage. Even though AA is recognized as an appropriate antioxidant and free radical scavenger, sometimes it can also behave as a pro-oxidant.\textsuperscript{7}

The aim of the present study was therefore to investigate the effect of different doses of vitamin C on oxidative liver injury due to INH in rats.

**Methods**

**Animals and study groups**

Male Wistar-Albino rats weighing 230–270 g obtained from University of Istanbul Animal Research Laboratory were kept in the same unit and fed chow ad libitum. All rats had free access to tap water and received humane care in compliance with the National Institutes of Health criteria for care of laboratory animals.

Rats were divided into four subgroups, each containing 10 rats. Of these four groups, three were used as experimental groups, and the other as a control group. Group 1 was the control group; group 2, INH 50 mg/kg per day; group 3, INH 50 mg/kg per day + low-dose vitamin C (100 mg/kg per day); group 4, INH 50 mg/kg per day + high-dose vitamin C (1000 mg/kg per day). INH and vitamin C were administered into their stomachs through an oral tube. The INH dose was substantially higher than that used for the treatment of tuberculosis in children, it was selected because it has been used in many animal studies carried out with INH.\textsuperscript{1,3,4,6}

All rats were killed at 3 weeks under ketamine anesthesia. After exploration of the thorax, intracardiac blood and liver samples were quickly obtained. The GSH levels in erythrocytes and biochemical variables were measured immediately. For the remaining studies, serum and liver tissue samples were stored at −80°C.

**Tissue homogenization**

Liver tissue samples were weighed as wet weight using a sensitive scale. The liver tissue samples were homogenized and diluted to 20% with 0.15 mol/L KCl. The resulting tissue homogenates were subsequently exposed to moderate sonication twice at intervals of 30 s. Following the sonication process, the homogenates were subsequently exposed to moderate sonication twice to prevent beta-type error (\(\alpha\) [significance level]/n [no. comparisons]). In this test, six comparisons were performed for the significant variables between four groups, and the relevant value was determined as 0.05 / 6 = 0.008 for the present study. Therefore, the variables with \(P < 0.008\) were considered significant for comparison.

**Biochemistry**

**Glutathione**

A yellow compound composed of the reagent 5,5′-ditiobis-2-nitrobenzoic acid and sulphhydryl was read at 412 nm.\textsuperscript{8} The results are given as mg/g Hb for the erythrocytes, and as mg/g protein for the liver tissue.

**Glutathione peroxidase**

This is based on the reduction of the oxidized form of GSH, which was formed by reactions with GSH-px and GSH reductase, and an NADPH is used during this reaction. The erythrocyte and tissue GSH-px levels were measured using commercial kits (Cat No: RS 505; Randox-Ransel, Krefeld, Germany).

**Lipid peroxidation and malondialdehyde**

Malondialdehyde, the end-product of lipid peroxidation, was measured in tissue and plasma samples on high-performance liquid chromatography (HPLC) using a commercial kit (Chromsystems, ✘, Germany). The MDA values are given as nmol/mL for plasma, and as nmol/100 mg protein for tissue.

**Superoxide dismutase**

The plasma and tissue SOD activity was measured according to the method of Sun et al., which is based on the blockade of the reduction of nitroblue tetrazolium by the superoxide-forming xanthine/xanthine oxidase.\textsuperscript{9}

**Vitamin C level**

Vitamin C was measured in the tissue and plasma samples on HPLC using a commercial kit (Chromsystems).

**Other biochemistry**

The levels of other biochemical variables in blood, for example alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT) were measured using an autoanalyzer (CX9 PRO; Beckman Coulter, Fullerton, CA, USA).

**Statistical evaluation**

The data obtained from the experimental procedures were statistically evaluated in two steps. In the first step, the difference between the four groups was assessed. Kruskal–Wallis test was used for the subgroup analysis of the significant variables. Because of the small number of subjects, a Bonferroni correction was used in the paired analysis to prevent beta-type error (\(\alpha\) [significance level]/n [no. comparisons]). In this test, six comparisons were performed for the significant variables between four groups, and the relevant value was determined as 0.05 / 6 = 0.008 for the present study. Therefore, the variables with \(P < 0.008\) were considered significant for comparison.

**Results**

**Serum aspartate aminotransferase**

Group 1 (153.8 ± 33.98 IU/L) was compared with group 2 (552.0 ± 100.38 IU/L), AST levels were significantly higher in group 2 (\(P < 0.008\)). When compared to group 2, groups 3 (139.4 ± 29.49 IU/L) and 4 (131.9 ± 26.89 IU/L) had significantly lower AST levels (\(P < 0.008\)). There was no statistically significant difference for AST levels between group 1 and groups 3 and 4 (\(P = 0.393\) and 0.218, respectively; Table 1).

**Serum alanine aminotransferase**

When group 1 (34.20 ± 5.22 IU/L) was compared with group 2 (71.50 ± 30.18 IU/L), ALT levels were significantly higher in...
group 2 ($P < 0.008$). When compared to group 2, groups 3 (4.19 ± 7.83 IU/L) and 4 (49.10 ± 6.26 IU/L) had significantly lower ALT levels ($P < 0.008$; Table 1).

**Serum γ-glutamyl transpeptidase**

When group 1 (2.9 ± 1.37 IU/L) was compared with group 2 (5.10 ± 1.44 IU/L), GGT levels were significantly higher in group 2 ($P < 0.008$). There was no statistically significant difference in GGT levels between group 1 and groups 3 (3.90 ± 1.72 IU/L) and 4 (4.20 ± 1.13 IU/L; $P = 0.190$ and 0.143, respectively; Table 1).

**Serum alkaline phosphatase**

There was no statistically significant difference in ALP level between the four groups ($P = 0.618$; Table 1).

**Serum and tissue MDA**

Serum MDA levels were significantly higher in group 2 (2.06 ± 0.21 nmol/mL) compared to group 1 (0.80 ± 0.13 nmol/mL; $P < 0.008$). The MDA level in groups 3 (1.00 ± 0.18 nmol/mL) and 4 (1.54 ± 0.43 nmol/mL) was significantly lower than that in group 2 ($P < 0.008$ for both). The MDA levels in the liver tissue were significantly higher in group 2 (0.64 ± 0.086 nmol/mg protein) compared to group 1 (0.50 ± 0.094 nmol/mg protein; $P < 0.008$). When compared to group 2, the MDA levels had a significant and non-significant decrease in groups 3 (0.49 ± 0.061 nmol/mg protein) and 4 (0.55 ± 0.082 nmol/mg protein), respectively ($P < 0.008$ and 0.035, respectively; Table 2).

**Serum and tissue SOD**

There was no statistically significant difference in the serum and tissue SOD levels between the four groups ($P = 0.095$; Table 3).

**Blood (erythrocyte) and tissue glutathione**

Blood GSH levels were significantly lower in group 2 (3.97 ± 0.42 mg/g Hb) compared to group 1 (5.08 ± 0.51 mg/g Hb; $P < 0.008$). When group 2 was compared with group 3 (4.76 ± 0.49 mg/g Hb), GSH levels were significantly higher in group 3 ($P < 0.008$). When group 2 was compared with group 4 (4.23 ± 0.34 mg/g Hb) there was no statistically significant difference ($P = 0.123$). GSH levels were significantly lower in group 4 than in group 1 ($P < 0.008$). The liver tissue GSH levels were found to be significantly lower in group 2 (29.80 ± 1.56 µg/mg protein) compared to group 1 (50.07 ± 4.31 µg/mg protein; $P < 0.008$). When group 2 was compared with group 3 (32.90 ± 3.03 µg/mg protein), GSH levels were significantly higher in group 3.

### Table 1  Serum AST, ALT, GGT, ALP levels (mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>GGT (IU/L)</th>
<th>ALP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Control), n = 10</td>
<td>153.8 ± 33.98</td>
<td>34.20 ± 5.22</td>
<td>2.9 ± 1.37</td>
<td>189.50 ± 41.34</td>
</tr>
<tr>
<td>Group 2 (INH alone), n = 10</td>
<td>552.0 ± 100.38</td>
<td>71.50 ± 30.18</td>
<td>5.10 ± 1.44</td>
<td>224.70 ± 93.53</td>
</tr>
<tr>
<td>Group 3 (INH + low-dose vitamin C), n = 10</td>
<td>139.4 ± 29.49</td>
<td>41.90 ± 7.83</td>
<td>3.90 ± 1.72</td>
<td>255.50 ± 123.62</td>
</tr>
<tr>
<td>Group 4 (INH + high-dose vitamin C), n = 10</td>
<td>131.9 ± 26.89</td>
<td>49.10 ± 6.26</td>
<td>4.20 ± 1.13</td>
<td>224.60 ± 60.07</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; INH, isoniazid.

### Table 2  Lipid peroxidation (MDA) and non-enzymatic (GSH) antioxidant activity (mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lipid peroxidation (MDA)</th>
<th>GSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum MDA (nmol/mL)</td>
<td>Liver tissue MDA (nmol/100 mg protein)</td>
</tr>
<tr>
<td>Group 1 (Control), n = 10</td>
<td>0.80 ± 0.13</td>
<td>0.50 ± 0.094</td>
</tr>
<tr>
<td>Group 2 (INH alone), n = 10</td>
<td>2.06 ± 0.21</td>
<td>0.64 ± 0.086</td>
</tr>
<tr>
<td>Group 3 (INH + low-dose vitamin C), n = 10</td>
<td>1.00 ± 0.18</td>
<td>0.49 ± 0.061</td>
</tr>
<tr>
<td>Group 4 (INH + high-dose vitamin C), n = 10</td>
<td>1.54 ± 0.43</td>
<td>0.55 ± 0.082</td>
</tr>
</tbody>
</table>

GSH, glutathione; INH, isoniazid; MDA, malondialdehyde.

### Table 3  Serum, blood (erythrocyte) and liver tissue antioxidant enzyme activities (mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOD</th>
<th>GSH-px</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum (U/mL)</td>
<td>Liver tissue (U/mg protein)</td>
</tr>
<tr>
<td>Group 1 (Control), n = 10</td>
<td>21.28 ± 1.60</td>
<td>0.58 ± 0.11</td>
</tr>
<tr>
<td>Group 2 (INH alone), n = 10</td>
<td>18.85 ± 1.95</td>
<td>0.47 ± 0.087</td>
</tr>
<tr>
<td>Group 3 (INH + low-dose vitamin C), n = 10</td>
<td>20.91 ± 2.11</td>
<td>0.49 ± 0.085</td>
</tr>
<tr>
<td>Group 4 (INH + high-dose vitamin C), n = 10</td>
<td>19.03 ± 2.16</td>
<td>0.48 ± 0.072</td>
</tr>
</tbody>
</table>

GSH-px, glutathione peroxidase; INH, isoniazid; SOD, superoxide dismutase.

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Table 4  Plasma and liver tissue vitamin C (AA) levels (mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vitamin C (AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma (mg/L)</td>
</tr>
<tr>
<td>Group 1 (Control), n = 10</td>
<td>4.92 ± 0.43</td>
</tr>
<tr>
<td>Group 2 (INH alone), n = 10</td>
<td>3.74 ± 0.36</td>
</tr>
<tr>
<td>Group 3 (INH + low-dose vitamin C), n = 10</td>
<td>4.67 ± 0.39</td>
</tr>
<tr>
<td>Group 4 (INH + high-dose vitamin C), n = 10</td>
<td>4.99 ± 0.40</td>
</tr>
</tbody>
</table>

AA, ascorbic acid; INH, isoniazid.

(P < 0.008). When group 3 was compared with group 1, there was no significant difference (P = 0.028; Table 2).

**Blood (erythrocyte) and tissue GSH-px**

Blood GSH-px levels were significantly lower in group 2 (12.39 ± 2.13 U/g Hb) than in group 1 (17.93 ± 2.52 U/g Hb; P < 0.008). When compared to group 2, blood GSH-px levels were significantly higher in group 3 (17.16 ± 1.22 U/g Hb; P < 0.008). Interestingly, when group 3 was compared with group 4, blood GSH-px levels were significantly higher in group 3 (P < 0.008). The liver tissue GSH-px levels were significantly lower in group 2 (1.36 ± 0.34 U/mg protein) than in group 1 (1.99 ± 0.28 U/mg protein; P < 0.008; Table 3).

**Plasma and tissue vitamin C (ascorbic acid)**

Plasma AA levels were significantly lower in group 2 (3.74 ± 0.36 mg/L) than in group 1 (4.92 ± 0.43 mg/L; P < 0.008). When compared to group 2, plasma AA levels were significantly higher in groups 3 (4.67 ± 0.39 mg/L) and 4 (4.99 ± 0.40 mg/L; P < 0.008 for both). Tissue AA levels were significantly lower in group 2 (0.44 ± 0.069 µg/mg protein) than in group 1 (0.72 ± 0.095 µg/mg protein; P < 0.008). When compared to group 2, tissue AA levels were significantly higher in groups 3 (0.60 ± 0.09 µg/mg protein) and 4 (0.75 ± 0.099 µg/mg protein; P < 0.008 for both; Table 4).

**Discussion**

Since its discovery in 1952, INH has been the most used drug in the treatment of tuberculosis. Initially, although it has been considered a highly reliable drug especially for children, hepatotoxicity associated with this drug started to be reported from the 1970s. Mitchell et al. observed that there was no relationship between the plasma level of INH and the INH-induced hepatotoxicity, and that toxicity was due to the drug’s metabolites (particularly acetyl hydrazine). They also reported that hepatotoxicity was more marked in those who acetylate the drug faster. In later studies, however, in 1976 and 1984, Ellard reported that there was no relationship between hepatotoxicity and the acetylation rate of INH (rapid-slow acetylators). Gurumurthy et al., in their retrospective review of 3000 patients who had been treated with INH, did not observe any relationship between hepatotoxicity and acetylation rate.

Data from other studies indicating that hepatotoxic drugs such as carbon tetrachloride (CCl4) and paracetamol lead to oxidative stress, thus causing liver damage, have suggested that an increase in the variables of oxidative stress and a decrease in antioxidants may also be responsible for the INH-induced liver damage. The mechanism by which the liver damage occurs has not been clearly demonstrated, although there a relationship has been detected between liver damage and the INH metabolites (hydrazine or acetyl hydrazine). In the present study the INH dose to be given through the nasogastric tube was determined as 50 mg/kg per day. Although this dose is substantially higher than that used for the treatment of tuberculosis in children, it was selected because it has been used in many animal studies carried out with INH.

In a study by Sodhi et al. they administered INH and rifampicin i.p. at a dose of 50 mg/kg per day to rats. At the end of 2 weeks of treatment they observed a significant increase in both the serum levels of ALT and AST and the serum bilirubin levels compared to the control group. The serum ALT and AST levels observed in the control group in the present study were similar to those in the control groups of other studies. In the rats given INH alone, we observed that the serum levels of ALT and AST were markedly higher than in the control group. In the Sodhi et al. study they also assessed the oxidant–antioxidant variables and observed a significant decrease in the hepatic levels of thiols, SOD, CAT, GSH-px and a decrease in the serum levels of GSH, GSH-px and CAT.

In another study by Attri et al., they administered INH + rifampicin into the peritoneum of rats. At the end of 3 weeks they observed a decrease in the serum levels of GSH, SOD, GSH-px and CAT, and an increase in the serum MDA levels. In that study N-acetyl cysteine, an antioxidant, was given to another group treated with INH + rifampicin, and no hepatic changes were observed, nor any decrease in the antioxidant levels. Similarly, we observed a decrease in both serum and hepatic levels of GSH-px and GSH and an increase in the serum MDA levels compared to the control group. The only difference from the aforementioned two studies was that the decrease in the serum and hepatic levels of SOD was not statistically significant in the present study. In another study by Sodhi et al., however, the serum levels of SOD were not different between the INH-treated group and the control group, supporting the present results.

It has been suggested that the reason for the difference between the serum levels of SOD observed in the different studies may be related to the superoxide radical and hydrogen peroxide balance. INH is a strong stimulator of the cytochrome P450 2E1 (CYP2E1) enzyme. In an experiment conducted with rats by Yue et al., in which hepatotoxicity was developed by administering INH, they found a positive correlation between the levels of ALT, plasma hydrazine and CYP2E1, and reported that the stimulation of CYP2E1 with hydrazine plays an important role in hepatotoxicity. CYP2E1 is also an enzyme that produces superoxide and hydroxyl radicals. The superoxide radicals, which are produced in great numbers, increase the activity of the SOD enzyme, whereas they make GSH-px and CAT ineffective. Excessive hydrogen peroxide (H2O2) occurring as a result of the two
enzymes being ineffective may have an adverse effect on SOD.\textsuperscript{19,20} Therefore, the SOD level may be higher, normal or lower due to the balance between the superoxide radicals and \( \text{H}_2\text{O}_2 \).

Previous studies have investigated the relationship between oxidative stress and liver damage.\textsuperscript{21–23} In the literature there is no report on the vitamin C levels in INH-induced liver injury. A substantial decrease in the AA levels within leukocytes has been detected in primary biliary cirrhosis.\textsuperscript{24} Similarly, the plasma AA levels have been found to be low in the patients with chronic active hepatitis, and those with hepatic cirrhosis and hepatocellular carcinoma.\textsuperscript{25} For the first time, both plasma and hepatic tissue levels of AA were found to be substantially low in rats, in the present study. An animal study by Matsuki \textit{et al.} demonstrated that AA administration combined with INH reduces the radical structures of hydrazine, the most important hepatotoxic metabolite of INH.\textsuperscript{26} In the present study the reason for the decrease in the hepatic and serum vitamin C levels in rats treated with INH may be either that AA reacts with the radical structures of INH’s toxic metabolites, thereby destroying them through its antioxidant effect, as demonstrated by the aforementioned study, or because there is an excessive consumption of AA due to non-enzymatic reactions during the removal of the toxic radicals, which are formed due to the INH administration.

Although AA is considered a suitable antioxidant and free radical scavenger, it may sometimes act as a pro-oxidant.\textsuperscript{7} In a study by Seo and Lee an animal model of hepatic ischemia–reperfusion was created using rats, and AA was administered intravascularly at doses of 30–100 mg/kg and 1000 mg/kg.\textsuperscript{27} At low doses such as 30 and 100 mg/kg an improvement was observed in the transaminases, the levels of MDA, the biliary flow, and the microsomal enzymes, whereas at high doses (1000 mg/kg) these variables worsened compared to the control group; and authors have suggested that high doses of AA may have pro-oxidant effects.\textsuperscript{27} Considering these findings, we used two other groups, besides the control group and the INH-alone group, to which we administered INH + low-dose and INH + high-dose AA, and found that in the group receiving INH + low-dose AA, there was an improvement in the levels of transaminases, GSH, MDA and GSH-px compared to the INH-alone group. Whereas in the group receiving high-dose AA, there was an improvement in the levels of transaminases and MDA compared to the INH-alone group, and the blood and tissue levels of GSH did not show any improvement, but even worsened. In conclusion, the use of vitamin C at a low dose may be a protective strategy that would decrease INH-induced liver damage in humans. When vitamin C is taken at very high doses, its antioxidant effect is not greater compared to the low doses. Moreover, it may reduce the blood levels of GSH.

Acknowledgment

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References

