

Research Article

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Pulmonary Protective Effects of Propofol on Cisplatin-Induced Oxidative Damage in Male Rats

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Abstract

Background: The present study was performed to investigate the protective effects of propofol against cisplatin-induced pulmonary toxicity in rats.

Methods: A total of 20 male Wistar rats weighing 180-250 g were divided into four groups of control, the cisplatin-intoxicated group intraperitoneally (IP) injected with cisplatin (7 mg/kg/d for a week), the propofol group (10 mg/kg/d, IP), and the protected group receiving propofol (10 mg/kg/d, IP) poisoned by cisplatin. Then, the biomarkers of total antioxidant capacity (TAC), catalase (CAT) activity, and lipid peroxidation (LPO) were measured in homogeneous lung tissues.

Results: The data revealed the evidence of oxidative stress in the lung tissue of cisplatin-intoxicated rats as indicated by an increase in the level of LPO compared with propofol and protected groups ($P < 0.05$). Moreover, TAC decreased in the cisplatin group while it increased in the propofol group compared to cisplatin and protected groups ($P < 0.05$). No significant difference was observed between the groups regarding CAT ($P > 0.05$). Protection with propofol ameliorated the oxidative stress induced by cisplatin in the lung tissue because of the reduction of LPO.

Conclusion: According to these results, it seems that propofol provides a remarkable protection against cisplatin-induced oxidative pulmonary damage mediated by its antioxidant properties.

Keywords: Cisplatin, Propofol, Antioxidants, Oxidative stress, Lung

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Introduction

Cisplatin (diamminedichloroplatinum (II)) is strongly believed to be one of the most important cytotoxic anticancer medications due to its broader efficacy in treating various types of cancer such as brain, neck, ovarian, lung, testicular, cervical, and breast (1). The primary cytotoxic mechanism is the formation of a DNA adduct (2). Along this line, cisplatin treatment has been linked to various toxic side effects including hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity, and nausea (3). These adverse effects of cisplatin-induced pulmonary damage have been attributed to increased lipid peroxidation (LPO) caused by free oxygen radicals and decreased antioxidant parameters (4). In previous research, cisplatin increased the amount of malondialdehyde (MDA), reduced enzymatic and nonenzymatic antioxidant levels, and caused severe DNA damage (5). Propofol (2,6 diisopropylphenol) is the most widely used hypnotic agent for induction anesthesia and is a mainstay in sedation in critically ill patients (6). Remarkably, some characteristics of propofol, including the rapid onset of hypnosis, titratability, short duration of action, rapid elimination, and minimal effects on evoked potentials make it ideal for general anesthesia, monitored

anesthesia care, and total intravenous (IV) anesthesia. In addition, propofol causes the potentiation of GABA receptors and the antagonism of NMDA receptors (7). The chemical structure of propofol contains a phenolic hydroxyl group which is similar to that of α -tocopherol (vitamin E), which is a natural antioxidant. Based on the findings of another study, the antioxidant activity of propofol results was partly observed for the phenolic structure in vitro and in vivo (8). It was further shown that propofol antioxidant properties inhibit LPO, resulting in the removal of reactive oxygen species (ROS). Despite its sedative and anesthesia functions, propofol has some other applications such as the management of acute pain, an agent for preventing the exacerbations of chronic migraine headaches, and in opioid-induced hyperalgesia (8). The present study investigated the antioxidant characteristics of propofol against cisplatin-induced pulmonary toxicity in rats.

Materials and Methods

Chemicals

Trichloroacetic acid, tetraethoxypropane, 2,4,6-tripyridyls-tiazine (TPTZ), 2-thiobarbituric acid (TBA), n-butanol,

propofol (Propofol-Lipuro 1%: Braun Melsungen AG Germany), and cisplatin were used in this investigation. All reagents and other chemicals were purchased from Sigma-Aldrich Company (USA).

Animals and Treatment

In this experimental study, 20 male Wistar rats (weighting 180-250 g) were used and kept at a 12:12 hour light-dark cycle and temperature-controlled (20 ± 2) with free access to drinking water and standard laboratory chow. Animals were randomly divided into four groups (each including 5 rats) and then, treated intraperitoneally (IP) once a day for a week.

The design of these treatments resulted in four experimental groups including control, cisplatin, propofol, and protected (cisplatin with propofol) groups. Continually, propofol was administrated (10 mg/kg/d, IP) according to (9,10) alone or in combination with cisplatin (7 mg/kg/d, IP) according to (11,12). The control group received only normal saline. Finally, animals were killed 24 hours after the last dose of treatment and their lung tissue samples were taken and then homogenized in ice-cold phosphate buffers (50 mM, pH=7.4) appropriate for the measured parameter. The tissue homogenates were centrifuged at 5000 rpm for 20 minutes at 4°C, and the supernatants were extracted to analyze LPO, total antioxidant capacity (TAC), and catalase (CAT) activity levels (13).

Oxidative Stress Biomarker Assay

Oxidative biomarkers including LPO, TAC, and CAT were measured in lung homogenate.

Measurement of Lipid Peroxidation

In this method, the LPO product in the lung tissue was determined by the TBA reagent during an acid heating reaction expressing the amount of MDA productions. Finally, the calibration curve of the tetramethoxypropane standard solution was used to determine the concentration of TBA-MDA adduct in the sample (14).

Measurement of Total Antioxidant Capacity

In this protocol, TAC was calculated with the ferric reducing ability of homogenate assay. This process is based on the ability of lung homogenate in reducing Fe^{3+} to Fe^{2+} in the presence of TPTZ. In addition, the reaction between Fe^{2+} and TPTZ causes a blue color complex and the maximum absorption at 593 nm (15).

Measurement of Catalase

The enzyme CAT is regarded as a biochemical marker which is useful for evaluating the oxidative stress and ROS (16). CAT activity was measured by the absorbance decrease at 240 nm in a reaction medium containing H_2O_2 (10 mM) and sodium phosphate buffer (50 mM, pH=7.0) according to (17).

Statistical Analysis

The results were expressed as the mean $\pm$ standard error of the mean of at least three independent experiments performed two times or more. The data were analyzed by the one-way analysis of variance, followed by performing a *least significant difference* test to compare multiple groups. A *P* value <0.05 was considered statistically significant.

Results

Oxidative Stress Parameters

Lipid Peroxidation

Based on the results (Figure 1), cisplatin caused a noticeable increase in LPO compared with the control group ($P=0.011$) while propofol induced a significant decrease in LPO in comparison with the cisplatin group ($P=0.007$). Finally, coadministration of cisplatin and propofol led to a reduction in cisplatin-induced LPO ($P=0.006$).

Total Antioxidant Capacity

The obtained data (Figure 2) demonstrated that TAC reduced by cisplatin in comparison with the control group ($P=0.004$) whereas treatment with propofol increased

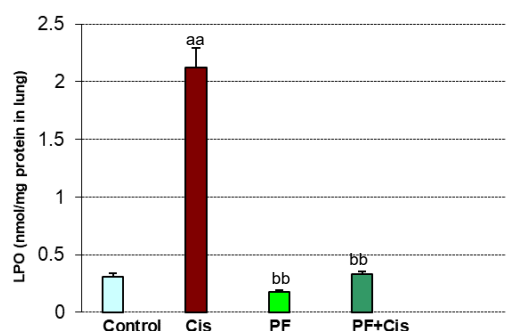


Figure 1. LPO in Lung Rats. Note. LPO: Lipid peroxidation; Pf: Propofol; Cis: Cisplatin; Pf + Cis: Propofol +cisplatin. Values are shown as the mean $\pm$ SE (n = 5). ^{aa} Significantly different from the control group at $P<0.05$; ^{bb} Significantly different from the Cisplatin group at $P<0.05$;

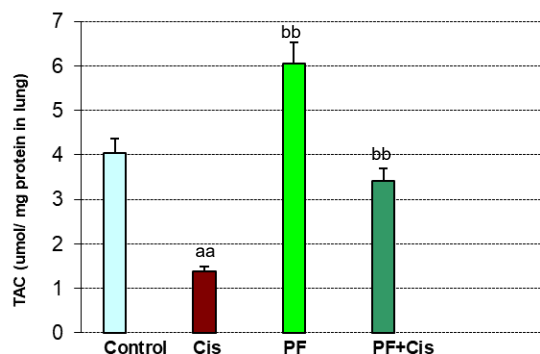


Figure 2. TAC in Lung Rats. Note. TAC: Total antioxidant capacity; CI: Confidence interval; Pf: Propofol; Cis: Cisplatin; Pf + Cis: Propofol +cisplatin. Values are indicated as the mean $\pm$ SE (n = 5). ^{aa} Significantly different from the control group at $P<0.05$; ^{bb} Significantly different from the Cisplatin group at $P<0.05$;

TAC compared with the cisplatin group ($P=0.001$). Eventually, coadministration of cisplatin and propofol remarkably increased the TAC level compared with the cisplatin group ($P=0.015$).

Catalase Activity

It is noteworthy that the CAT enzyme failed to show noticeable variations between the groups (Figure 3).

Discussion

Cisplatin-induced pulmonary damage was indicated by oxidative stress biomarkers. It seems that the biochemical mechanism of the injury of cisplatin and other platinum-based cytotoxic drugs is related to the production of intracellular ROS upon DNA (18). In this investigation, the biochemical tests revealed significantly increased levels of LPO and decreased levels of TAC with cisplatin toxicity. Further, the result showed that propofol attenuated cisplatin-induced lung injury, which may be associated with its antioxidant properties. In normal conditions, a balance is observed between oxidant and antioxidant levels in the system. According to evidence, cisplatin leads to the generation of free radicals, causing an increase in cell membrane LPO and the overproduction of MDA. Furthermore, it has been reported that tissue injury can be associated with a notable decrease in antioxidant defense mechanisms involved in the pathogenesis of cisplatin-induced oxidative damage (4). In a similar study, Afsar et al reported that MDA and H_2O_2 levels increased whereas the level of *glutathione* and other enzymatic antioxidants decreased in the presence of cisplatin-induced lung damage (5). Likewise, Leo et al found that cisplatin chemotherapy-induced structural pulmonary damage associated with fibrosis, interstitial inflammation, and destructive bronchiolitis (19).

On the other hand, propofol indicates antioxidant properties through a reduction in oxidative stress induced by cisplatin, and the result of the present study confirmed this issue because of the reduction of LPO in the protection group poisoned by cisplatin. According to

some studies (20-23), flavonoids, vitamin E, and vitamin C exhibit their antioxidant activity by different mechanisms (e.g., by scavenging radicals). Remarkably, the antioxidant characteristics of propofol can be due to its capacity in diminishing LPO (24), activating the expression of antioxidant enzyme home oxygenase-1 (25), decreasing the expression of nitric oxide synthase (26), and fixing the mitochondrial membrane (27). Meanwhile, previous research demonstrated that propofol has effective efficacy against acute lung injury in rats (28). Recently, it has been reported that propofol ameliorates the acute lung injury in neonatal rats with lipopolysaccharide-induced lung injury by preventing inflammations such as *tumor necrosis factor- α* , *interleukin* (IL)-6, and IL-1 β and oxidative stress (29).

Because of high lipophilicity, propofol penetrates to mitochondria, accepting electrons and disrupting the electron transport chain at the level of coenzyme Q (30). Therefore, propofol leads to a failure in *adenosine triphosphate* production inhibiting the mitochondrial fatty acid metabolism, causing the buildup of fatty acids (30,31). These disruptions caused to emerge the term 'propofol infusion syndrome', which is the prolonged infusion of propofol (> 4 mg/kg/h for more than 24 hours). The syndrome presents with metabolic acidosis, hyperlipidemia, hyperkalemia, and rhabdomyolysis (32).

To the best of our knowledge, propofol not only acts as a scavenger of free radicals and thus protects the body but also has been shown to increase the antioxidant activity of human plasma and protects cells from oxidative stress by impeding LPO (33). Additionally, propofol is shown to have some neuroprotective effects (34).

Having summarized all the point about the protective effects of propofol in cisplatin-induced pulmonary toxicity, according to the results of this investigation, cisplatin exposure results in a remarkable increase in LPO production by the generation of free radicals while propofol decreases the level of LPO because of its antioxidant property (Figure 1). Thus, it seems that cisplatin-induced oxidative damage could be improved by propofol, which justifies why it can prevent the sequence of oxidative stress.

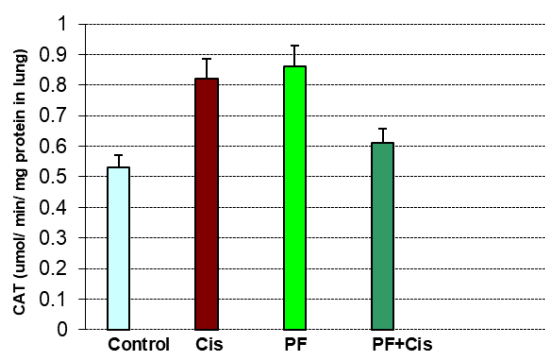


Figure 3. CAT in Lung Rats. Note. CAT: Catalase activity; CI: Confidence interval; Pf: Propofol; Cis: Cisplatin; Pf + Cis: Propofol +cisplatin. Values are represented as the mean $\pm$ SE ($n = 5$).

Conflict of Interests

The authors report no conflict of interests.

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