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Environmental Toxicology and Pharmacology 26 (2008) 49–55
ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY ETAP
www.elsevier.com/locate/etap

Protective effects of ligustrazine on cisplatin-induced oxidative stress, apoptosis and nephrotoxicity in rats

Xiao-hua Liu [a], Jin Li [b], Qi-xiong Li [a,*], Yong-xun Ai [c], Li Zhang [a]

[a] *Department of Pharmacology, Basic Medical School of Wuhan University, Wuhan 430071, China*
[b] *Department of Laboratory, Zhongnan Hospital of Wuhan University, Wuhan 430071, China*
[c] *Department of Pharmacology, Medical School of Jianghan University, Wuhan 430056, China*

Received 26 October 2007; received in revised form 19 January 2008; accepted 21 January 2008
Available online 3 February 2008

Abstract

Cisplatin is an effective agent against various solid tumors. However, its nephrotoxicity been reported to be a dose-limiting factor for treating various types of tumors. The aim of this study was to determine the protective effects of ligustrazine on cisplatin-induced nephrotoxicity through tissue oxidant/antioxidant parameters, light microscopic evaluation, and tubular apoptosis in rats. Ligustrazine was administered in doses of 50 and 100 mg/kg/day intraperitoneally (i.p.), for 7 consecutive days, starting 2 days before a single intraveneous dose of cisplatin (8 mg/kg). Results revealed that treatment with cisplatin alone caused significant changes in the levels of urinary protein, urinary *N*-acetyl-beta-D-glucosaminidase, serum creatinine, blood urea nitrogen, and kidneys histopathological damages. All the aforementioned changes were effectively attenuated by ligustrazine. In addition, cisplatin caused increases in the levels of malondialdehyde, nitric oxide, nitric oxide synthase and decreases in the levels of reduced glutathione, glutathione-*S*-transferase, superoxide dismutase. These changes were restored to near normal levels by ligustrazine at 100 mg/kg. In conclusion, ligustrazine has dose dependent protective effects against cisplatin-induced renal tubular toxicity.

Keywords: Ligustrazine; Cisplatin; Nephrotoxicity; Antioxidant; Apoptosis

1. Introduction

Although cisplatin (*cis*-diamminedichloroplatinum) is one of the most widely used anti-cancer drugs effective in treating a range of neoplastic diseases, several toxic effects of this drug are known in humans and animals. Cisplatin is associated with adverse drug reactions including renal damage and gastrointestinal dysfunction (Mishima et al., 2006). However, the major dose-limiting side effect of cisplatin is its nephrotoxicity (Badary et al., 2005; Kawai et al., 2006). This nephrotoxicity can results in severe nephropathy leading to acute renal failure (Kang et al., 2004; Kawai et al., 2006). The nephrotoxicity of cisplatin is associated with cell membrane peroxidation, mitochondrial dysfunction, inhibition of protein synthesis, DNA damage, changes in the pro-apoptotic *Bax* protein and inhibition of the antioxidant system by pro-oxidant damage to the renal tissue (Lee et al., 2001; Sheikh-Hamad et al., 2004; Wu et al., 2005). Previous reports have demonstrated protective roles for antioxidants and free radical scavengers such as vitamin E, lipoic acid, ebselen, and *N*-acetylcysteine in cisplatin-induced acute nephrotoxicity (Hussain et al., 1998; Davis et al., 2001).

Chinese herbs are natural therapeutic agents based on the principles of traditional Chinese medicine. They have been extensively used in China to treat human diseases for centuries. People are becoming increasingly interested in traditional Chinese medicines because of their low toxicity and their effectiveness in treating various diseases. Ligustrazine (tetramethypyrazine), a bioactive component contained in Chuanxiong (*Ligusticum chuanxiong Hort*), is widely used in the treatment of cardiovascular diseases in China such as myocardial and cerebral infarction (Li et al., 2006). It has been reported that ligustrazine can increase coronary blood flow and reduce myocardial ischemia in animals (Dai and Bache, 1985). Previous reports showed that ligustrazine-mediated vascular relaxation were both Ca^{2+} and ATP-dependent (Tsai et al., 2002). It blocks calcium channels, reduces the bioactivity of platelets and platelet aggregation, and inhibits free radicals (Zou et al., 2001). In addition, ligustrazine has been demonstrated to play a protective role in

* Corresponding author. Tel.: +86 27 68758665.
E-mail address: xiongqili54321@163.com (Q.-x. Li).

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doi:10.1016/j.etap.2008.01.006

ischemia-reperfusion kidney injury in rats (Sun et al., 2002; Feng et al., 2004). Patients with proliferative glomerulonephritis showed signs of reduced progression of their disease after being treated with ligustrazine (Huang and Zhan, 1998). Based on previous published reports, the mechanism of ligustrazine may be due to its scavenging effect on superoxides (Liu et al., 2002).

In the presented study, we designed the following experiments to establish the protective effects of ligustrazine against cisplatin-induced nephrotoxicity in rats and the changes in oxidant/antioxidant status of renal cortex, renal tubule cell apoptosis, and apoptosis protein expression.

2. Materials and methods

2.1. Chemicals

Ligustrazine hydrochloride injection (2%) was purchased from Beijing Yongkang Pharmaceutical Co. Ltd. (Beijing, China). Apoptosis Measurement Kit (Boehringer Mannhelm Corp., Mannheim, Germany), The *bcl-2* monoclonal antibody and *Bax* polyclonal antibodies & biotinylated goat anti-rabbit IgG Kit were purchased from Beijing Zhongshan Biotechnology Co. Ltd. (Beijing, China). Cisplatin and all other chemicals were obtained from Sigma (St. Louis, MO, USA).

2.2. Experimental animals

Male Sprague–Dawley rats (8-week-old weighing 180 ± 20 g) were obtained from Wuhan University Experimental Research Centre, Wuhan, China and approved by the Animal Care Committee of Wuhan University. The animals were housed in standard cages at room temperature (20–24 °C) and regular light cycle (12 light/12 dark). Food and drinking water (from water bottles) were available *ad libitum*.

2.3. Experimental design

Rats were divided into four groups of eight animals each. Control group: rats were injected i.v. through a tail vein with 0.9% saline (10 ml/kg). Cisplatin group: rats were injected i.v. a single dose of cisplatin (8 mg/kg). Cisplatin plus ligustrazine (50 and 100 mg/kg) group: rats were injected i.v. respectively a single dose of cisplatin (8 mg/kg). Ligustrazine was given i.p. once daily at 50 and 100 mg/kg for 7 days starting 2 days before singly i.v. cisplatin. Control and cisplatin-treated rats were administered i.p. once daily 0.9% saline in the same volume for 7 days.

The animals were allowed to acclimatize to the metabolic cages for 2 days before beginning the experiments. 24-h urine was collected at the 5th day after administration of cisplatin to measure the content of urinary protein and urinary *N*-acetyl-beta-D-glucosaminidase (NAG) levels. At the end of the experiments, the animals in all groups were anesthetized with 45 mg/kg sodium pentobarbital and were sacrificed 4 h after the last administration. Blood samples were collected to measure serum creatinine and blood urea nitrogen. The samples were centrifuged at 200 × *g* for 5 min at +4 °C. Kidneys were removed rapidly, sectioned for histological and immunohistochemical analysis. The remaining kidney tissues were homogenized in Tris–HCl buffer (0.05 mol/l Tris–HCl, 1.15% KCl, pH 7.4), using a Polytron homogeniser. The homogenate was centrifuged at 18,000 × *g* (+4 °C) for 30 min, the supernatant was utilized for biochemical analysis.

2.4. Biochemical assays

Urinary protein content was measured according to the sulfosalicylic acid colorimetric method (Salant and Cybulsky, 1988). Urinary NAG activity was determined by colorimetric method utilizing 3-cresolsulphaphytaleinyl-*N*-acetyl-β-D-glucosaminide as substrate (Price, 1979). Serum creatinine and blood urea nitrogen concentrations were measured using an autoanalyzer (Beckman Instruments, Fullerton, CA, USA). The concentrations of the malondialdehyde (MDA) were determined according to the method based on the reaction with thiobarbituric acid (Ohkawa et al., 1979). Superoxide dismutase (SOD) activity was assayed in cytosolic fraction following the inhibition of pyrogallol autooxidation (Misra and Fridovich, 1972). Glutathione (GSH) level was measured colorimetrically as protein-free sulfhydryl content using 5,5-dithiobis-2-nitrobenzoic acid (DTNB) (Beutler et al., 1963). Glutathione-*S*-transferase (GST) activity was determined spectrophotometrically using 1-chloro-2, 4-dinitrobene (CDNB) as a substrate in the presence of GSH (Habig et al., 1974). Nitric oxide (NO) and nitric oxide synthase (NOS) levels were determined by a colorimetric method based on the Greiss Reaction (Stuehr et al., 1989). Total protein content was determined by Lowry method using bovine serum albumin as a standard (Lowry et al., 1951).

2.5. Histopathology

At the end of each experiment the kidneys were removed and fixed in 4% formaldehyde and embedded in paraffin. Sections were cut by a microtome at 4-μm-thickness, mounted on a cover class and stained with haematoxylin/eosin (HE). The histological sections were examined with a light microscope to evaluate kidneys tubular pathological changes.

2.6. Immunohistochemistry

Kidneys were fixed in 4% formaldehyde and embedded in paraffin. For each kidney, 4-μm cross-sections were cut by a microtome and mounted on to glass slides. Apoptosis was assessed by an in situ terminal deoxynucleotidyl-transferasemediated 2′-deoxyuridine 5′-triphosphate (dUTP) nick end labeling (TUNEL) technique. The procedure was performed according to the manufacturer's instructions. Briefly, slides were deparaffinized and rehydrated by serial changes of xylene and ethanol. The tissue was treated with 0.25% proteinase K (Sigma) in phosphate-buffered saline at room temperature for 20 min. To block endogenous peroxidase, the slides were incubated with 3% hydrogen peroxide in methanol for 20 min and then incubated with 300 U/ml of terminal deoxynucleotidyl transferase (TdT) and 20 μM biotin-16-dUTP in TdT buffer. The incubation was carried out in a humidified chamber at 37 °C for 60 min. On another slide, the TdT incubation was omitted to serve as a negative control. After end labeling, the section was incubated with avidin–biotin complex containing horseradish peroxidase, stained with diaminobenzidine, and counterstained with benatoxylin. When viewed under a light microscope, apoptotic nuclei stained brown, and non-apoptotic nuclei were blue (Liu et al., 2007). Apoptosis rate % = number of apoptotic cells/total cells × 100%.

To stain tissues with various antibodies, kidney tissues were fixed in 4% formaldehyde for 24 h and embedded in paraffin routinely, followed by 4-μm slicing up. The streptavidin peroxidase (SP) method was assumed (Gao and Zhou, 2005). The *bcl-2* monoclonal antibody (1:50) or *Bax* polyclonal antibody (1:50) was applied and incubated overnight at 4 °C or for 60 min at room temperature. The slices were observed and photographed through light microscope and positive cells were cytoplasm stained yellow brown.

2.7. Statistics

All results were expressed as mean ± standard deviations ($n = 8$). Differences between groups were assessed by the one-way analysis of variance (ANOVA) and *t*-test. Statistical significance was defined as $P < 0.05$.

3. Results

A single dose of cisplatin caused a significant increase in urinary protein and urinary NAG levels 5 days after the initial treatment. In contrast, pretreatment and co-administration of ligustrazine (50 and 100 mg/kg) significantly alleviated cisplatin-induced urinary protein and NAG changes (Table 1).

Rats treated with cisplatin alone showed significant elevation in both serum creatinine and blood urea nitrogen levels in com-

Table 1
Effects of ligustrazine on urinary protein and urinary NAG levels in cisplatin-induced nephrotoxicity

Group	Urinary protein mg/24 h urine	Urinary NAG U/g creatinine
Saline	1.16 ± 0.52	25.12 ± 5.92
Cisplatin	12.69 ± 5.74[a]	55.56 ± 8.24[a]
Cisplatin + ligustrazine (50 mg/kg)	7.43 ± 3.32[b]	46.15 ± 11.53
Cisplatin + ligustrazine (100 mg/kg)	4.40 ± 1.80[c]	39.53 ± 11.20[c]

Data given are the mean ± standard deviations ($n = 8$).
[a] Significantly different from saline control ($P < 0.01$).
[b] Significantly different from cisplatin control ($P < 0.05$).
[c] Significantly different from cisplatin control ($P < 0.01$).

Table 2
Effects of ligustrazine on blood urea nitrogen and serum creatinine contents in cisplatin-induced nephrotoxicity

Group	Blood urea nitrogen nmol/l	Serum creatinine μmol/l
Saline	5.6 ± 0.3	41.6 ± 9.2
Cisplatin	15.2 ± 2.5[a]	118.0 ± 18.0[a]
Cisplatin + ligustrazine (50 mg/kg)	12.4 ± 1.6[b]	101.0 ± 8.0[b]
Cisplatin + ligustrazine (100 mg/kg)	6.4 ± 1.2[c]	60.3 ± 9.6[c]

Data given are the mean ± standard deviations ($n = 8$).
[a] Significantly different from saline control ($P < 0.01$).
[b] Significantly different from cisplatin control ($P < 0.05$).
[c] Significantly different from cisplatin control ($P < 0.01$).

parison with the control group. Compared with cisplatin-treated group, pretreatment or co-administration of ligustrazine (50 and 100 mg/kg) showed dose-dependent inhibition in the elevation of serum creatinine and blood urea nitrogen levels induced by cisplatin (Table 2).

Kidney tissues in control rats showed normal glomerular and tubular structures (Fig. 1A). In contrast, cisplatin treatment caused significant morphological alterations, including tubular swelling and protein casts (Fig. 1B). Protein casts in the tubules were dramatically decreased in ligustrazine (50 mg/kg) treated group compared to the cisplatin treated group (Fig. 1C). Ligustrazine (100 mg/kg) significantly ameliorated tubular injury induced by cisplatin, the tubules showed only a few and slight protein casts (Fig. 1D). These results indicated that treatment with this compound afforded protection against cisplatin-induced renal tubular toxicity.

Antioxidation analysis showed that GSH levels and the levels of GST and SOD were lower while MDA, NO and NOS levels in kidney tissues were higher in the cisplatin treated group than those in control rats. Ligustrazine (50 mg/kg) had no effect on GSH, NO contents and GST, NOS levels, but reduced the effect of cisplatin on MDA content and SOD levels in kidney tissues. At a higher dose (100 mg/kg), ligustrazine significantly decreased MDA, NO and NOS levels while increased GSH content and

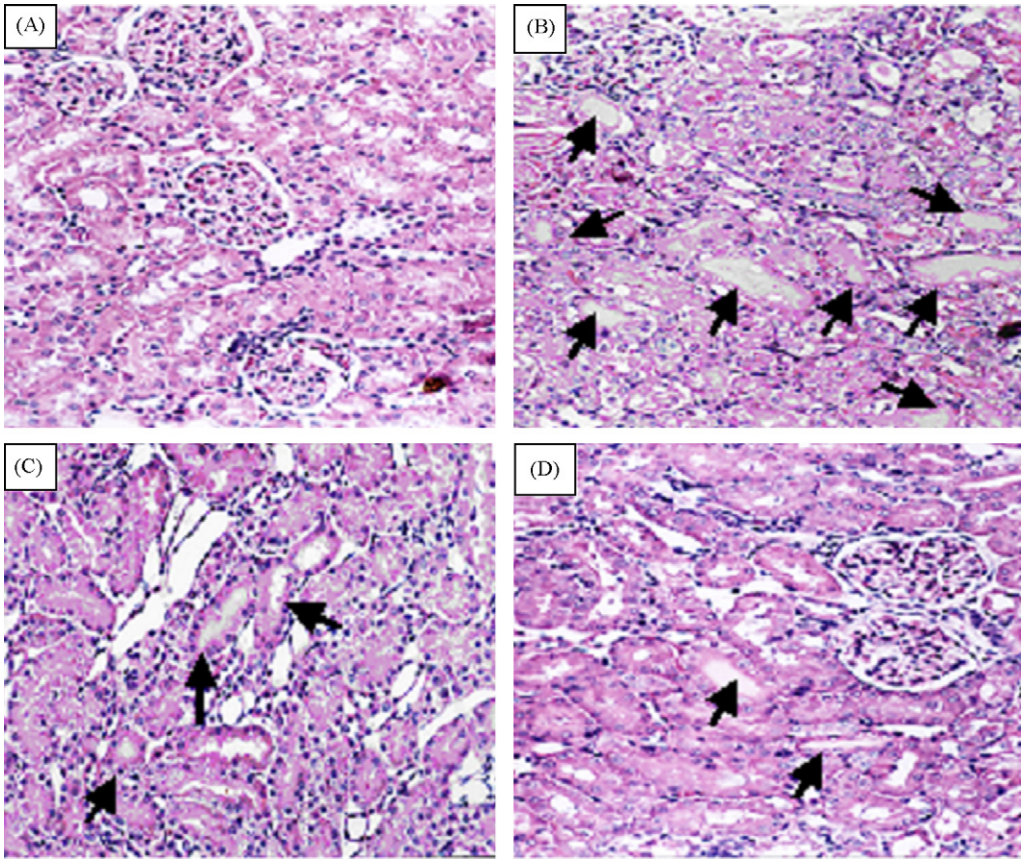

Fig. 1. Light microscopy of kidney tissues from rats (HE stained kidney sections, 200×). (A) Control group. (B) Cisplatin group: Tubules show extensive and marked swelling and protein casts (arrow). (C) Cisplatin + ligustrazine (50 mg/kg) group: Tubules show obvious decrease in protein casts (arrow). (D) Cisplatin + ligustrazine (100 mg/kg) group: tubules show only a few and slight protein casts (arrow).

Table 3
Effects of ligustrazine on kidneys GSH, GST, MDA, SOD, NO, NOS levels in cisplatin-induced nephrotoxicity

Group	GSH μmol/mg protein	GST μmol/mg protein	MDA μmol/mg protein	SOD μmol/mg protein	NO μmol/mg protein	NOS μmol//mg protein
Saline	17.21 ± 3.32	1.84 ± 0.63	0.31 ± 0.06	2.01 ± 0.44	0.11 ± 0.06	0.49 ± 0.09
Cisplatin	12.52 ± 3.55[a]	1.15 ± 0.60[a]	0.59 ± 0.17[b]	1.02 ± 0.30[b]	0.29 ± 0.07[a]	0.63 ± 0.07[a]
Cisplatin + ligustrazine (50 mg/kg)	12.80 ± 3.93	1.57 ± 0.63	0.36 ± 0.06[c]	1.89 ± 0.94[c]	0.20 ± 0.10	0.54 ± 0.16
Cisplatin + ligustrazine (100 mg/kg)	16.65 ± 3.06[c]	1.81 ± 0.39[d]	0.21 ± 0.04[d]	3.26 ± 0.63[d]	0.16 ± 0.08[d]	0.49 ± 0.12[c]

Data given are the mean ± standard deviations ($n = 8$).
[a] Significantly different from saline control ($P < 0.05$).
[b] Significantly different from saline control ($P < 0.01$).
[c] Significantly different from cisplatin control ($P < 0.05$).
[d] Significantly different from cisplatin control ($P < 0.01$).

SOD, GST activities when compared to the group treated with cisplatin alone (Table 3).

Immunohistochemical analysis demonstrated control rats had little kidney tubular cell apoptosis (Fig. 2A). In contrast, significant apoptosis was observed in the group treated with cisplatin (Fig. 2B). Ligustrazine (50 mg/kg) decreased kidney tubular cell apoptosis in cisplatin-treated rats (Table 4, Fig. 2C). When the dose of ligustrazine was increased to 100 mg/kg, its effect on cisplatin-induced apoptosis was more pronounced (Table 4, Fig. 2D). The expression of *Bax* protein in kidney tubular cells was much stronger and that of *Bcl-2* protein was weaker in the group of rats treated with cisplatin as compared to control (Figs. 3B and 4B). Ligustrazine (50 mg/kg) treated group had

Table 4
Effect of ligustrazine on cisplatin-induced kidney tubule cell apoptosis

Group	Apoptosis rate/%
Saline	0.35 ± 0.18
Cisplatin	7.52 ± 3.40[a]
Cisplatin + ligustrazine (50 mg/kg)	5.18 ± 1.93[b]
Cisplatin + ligustrazine (100 mg/kg)	0.58 ± 0.37[c]

Data given are the mean ± standard deviations ($n = 8$).
[a] Significantly different from saline control ($P < 0.01$).
[b] Significantly different from cisplatin control ($P < 0.05$).
[c] Significantly different from cisplatin control ($P < 0.01$).

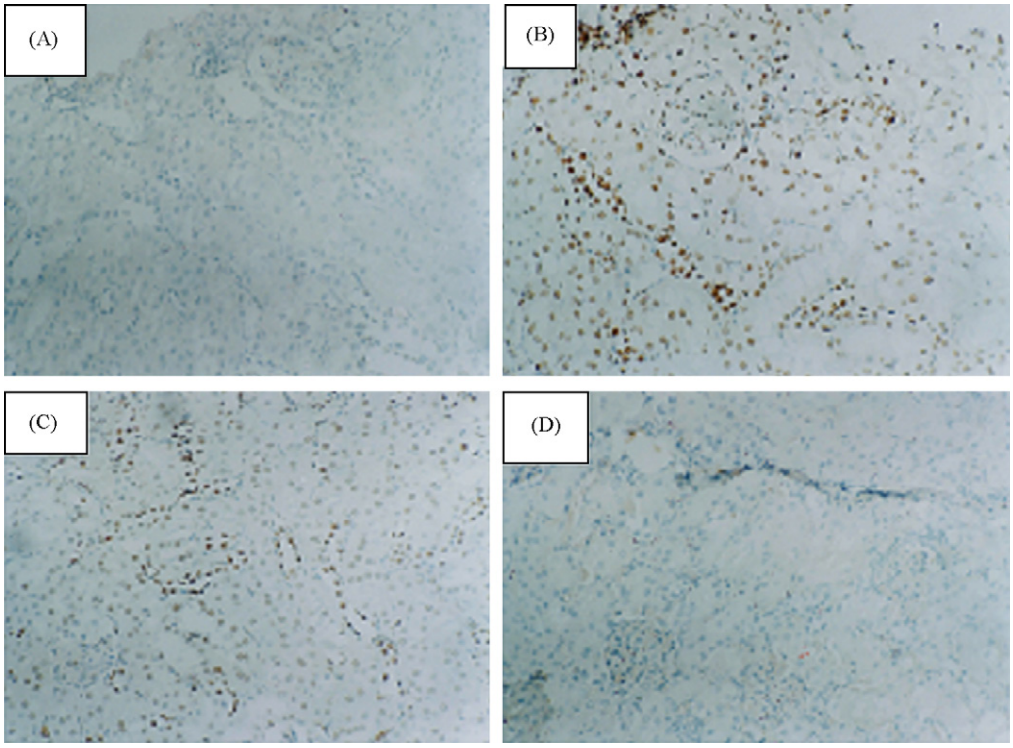

Fig. 2. Effect of ligustrazine on cisplatin-induced kidney tubular cell apoptosis (TUNEL, 400×). Apoptotic nuclei stained brown, non-apoptotic nuclei blue. (A) Control group: no kidney tubular cell apoptosis. (B) Cisplatin group: obvious kidney tubular cell apoptosis. (C) Cisplatin + ligustrazine (50 mg/kg) group: less kidney tubular cell apoptosis. (D) Cisplatin + ligustrazine (100 mg/kg) group: little kidney tubular cell apoptosis.

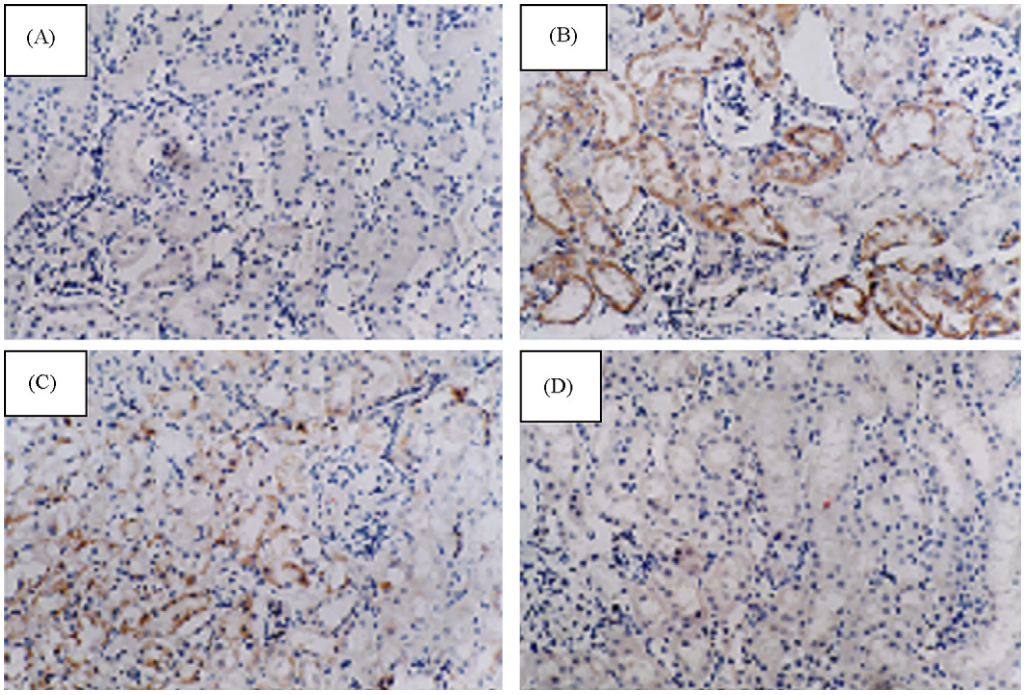

Fig. 3. Effect of ligustrazine on cisplatin-induced changes in the expression of kidney tubular cell *Bax* protein (SP, 400×). Cytoplasm was stained brown-yellow in *Bax* protein expression. (A) Control group: *Bax* was not expressed. (B) Cisplatin group: *Bax* expression was abundant. (C) Cisplatin + ligustrazine (50 mg/kg) group: *Bax* expression was weak. (D) Cisplatin + ligustrazine (100 mg/kg) group: *Bax* expression was very weak.

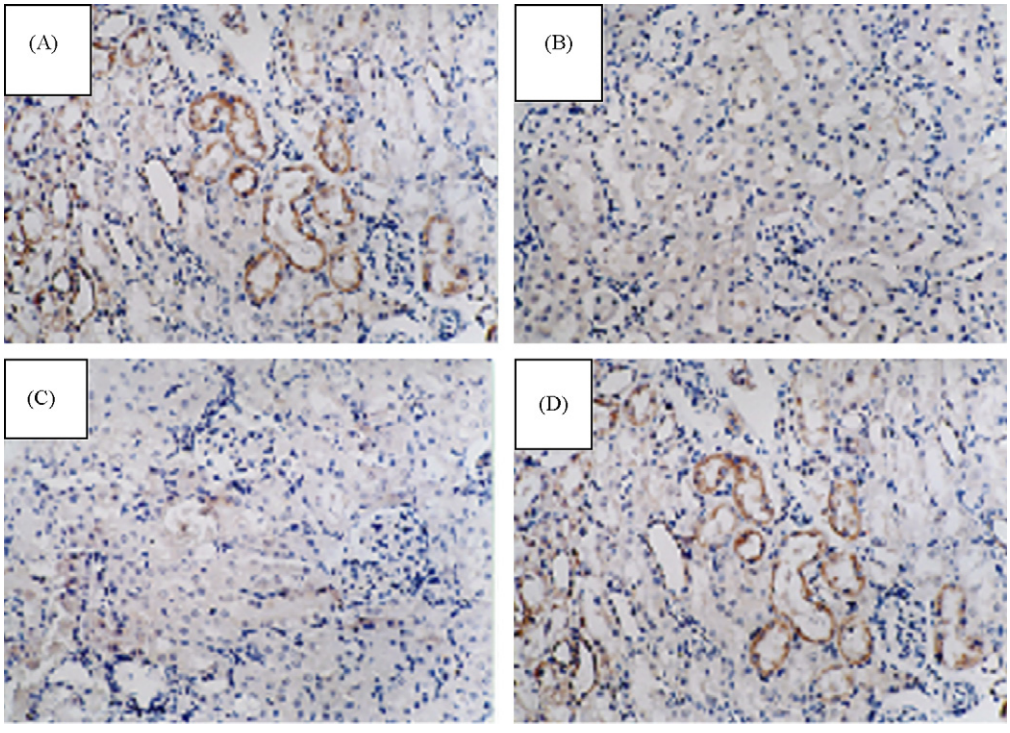

Fig. 4. Effect of ligustrazine on cisplatin-induced changes in the expression of kidney tubular cell *Bcl-2* protein (SP, 400×). Cytoplasm was stained brown-yellow in *Bcl-2* protein expression. (A) Control group: *bcl-2* expression was abundant. (B) Cisplatin group: little *bcl-2* expression. (C) Cisplatin + ligustrazine (50 mg/kg) group: *bcl-2* expression was weak. (D) Cisplatin + ligustrazine (100 mg/kg) group: expression of *bcl-2* was abundant.

slight effect changes of protein expression levels of *Bax* and *Bcl-2* induced by cisplatin (Figs. 3C and 4C) while that of ligustrazine at a higher dose (100 mg/kg) had a more dramatic effect (Figs. 3D and 4D).

4. Discussion

The nephrotoxicity of cisplatin is well documented as the most important dose-limiting factor in cancer chemotherapy.

Therefore, strategies of ameliorating the nephrotoxicity of cisplatin are of clinical interest. In this study, ligustrazine was shown to ameliorate the nephrotoxic effect of cisplatin in rats. Ligustrazine effectively reversed cisplatin-induced changes in urinary protein, urinary NAG, serum creatinine, blood urea nitrogen and kidney histopathological damages, making it a possible clinical candidate to prevent cisplatin nephrotoxicity related to cancer chemotherapy.

The mechanisms of cisplatin-induced renal tubular toxicity have not been fully understood. Several studies have shown that reactive oxygen species or free radicals are closely related to the nephrotoxicity induced by cisplatin (Baliga et al., 1998). Antioxidants and various free radical scavengers have been shown to be protective in cisplatin-induced nephrotoxicity. Glutathione, an endogenous free thiol, has been reported to decrease nephrotoxicity induced by cisplatin (Kunihiko et al., 2002). MDA is a parameter to measure lipid peroxidation and its increase is a direct result of free radical damage to membrane components of the cells. In the present study, we observed significant increases in the levels of MDA and a decrease in GSH concentrations in the kidney tissues of rats treated with cisplatin. The preventive effects of ligustrazine may be due to its free radical scavenging abilities because it effectively reversed the depletion of GSH and the decrease in GST and SOD antioxidant activities induced by cisplatin. The benefits of ligustrazine could also be attributed to its ability to reduce peroxidation of renal tubular cells, as it attenuated cisplatin-induced MDA increases.

A recent study showed that a certain basal amount of NO may be important for maintaining normal renal function (Fujihara et al., 2006). However, increasing evidence suggests that excessive production of NO plays a major role in oxidant stress and tissue damage in the pathophysiology of acute renal failure (Passauer et al., 2005). Ligustrazine has been shown to scavenge superoxide anion and NO in polymophonuclear leukocytes, and consequently to prevent the formation of peroxynitrite (Zhang et al., 2003a,b). Our data demonstrated the marked elevation in NO and NOS levels in damaged kidney tissue of the cisplatin-treated rats and ligustrazine (100 mg/kg) significantly attenuated these increments. Based on the importance of NO and NOS in acute renal failure in the rat, it appears that the inhibition of NO and NOS during cisplatin treatment may offer the protection against cisplatin nephrotoxicity. In our previous studies, ligustrazine was given i.p. once daily at 50 and 100 mg/kg for 15 days after a single i.v. dose of rabbit anti-rat glomerular basement membrane serum. Ligustrazine showed dose-dependent inhibition the elevation of urinary protein, serum creatinine and blood urea nitrogen as well as the development of glomerular histological changes. In that previous study, ligustrazine at a lower dose (50 mg/kg) had no effect on GSH content, glutathione peroxidase and catalase activities, but decreased the MDA content and increased SOD activity in nephritis induced by anti-glomerular basement membrane antibody. Ligustrazine at a higher dose (100 mg/kg) significantly decreased MDA content while dramatically increased GSH content and SOD, glutathione peroxidase, catalase activities of kidney tissues in the rat treated with anti-glomerular basement membrane antibody alone (Fu et al., 2007). Another potential mechanism for ligustrazine's protective effect could involve the suppression of TNF-alpha. Cisplatin nephrotoxicity appears to be mediated, at least in part, by induction of TNF-alpha in renal parenchymal cells (Zhang et al., 2007). Furthermore, Salicylate reduces cisplatin nephrotoxicity by inhibition of tumor necrosis factor-alpha (Ramesh and Reeves, 2004). Chang recently reported that Ligustrazine suppresses TNF-alpha and activated caspase-3 expression in middle cerebral artery occlusion-induced brain ischemia in rats (Chang et al., 2007).

Apoptosis plays an important role in the pathogenesis of a variety of renal diseases (Ueda et al., 2000). Intervention of cell apoptosis and apoptosis-related genes may be an effective method to prevent and cure renal diseases (Rana et al., 2001). Under pathological conditions, cisplatin activates multiple signaling pathways, resulting in necrosis and apoptosis of renal tubular cells (Park et al., 2002). Interaction of cisplatin with CYP2E1 results in the generation of reactive oxygen metabolites that causes renal injury and initiates apoptosis. Recent reports show that CYP2E1 null mice provide novel protection against cisplatin-induced nephrotoxicity and apoptosis (Liu and Baliga, 2003). In cultured tubular epithelial cells, cisplatin can activate the proapoptotic protein *Bax*, resulting in cytochrome *c* release, caspase activation, and apoptosis (Wei et al., 2007). Our study showed that cisplatin-induced apoptosis in kidney tubular cells. It significantly increased the expression of *Bax* protein and decreased the expression of *Bcl-2* protein. Our findings are in accordance with previous reports that cisplatin induces kidney tubular cell apoptosis and increases the expression of *Bax* protein in renal tissues (Sheikh-Hamad et al., 2004; Borrego et al., 2006). Ligustrazine significantly inhibited kidney tubular cell apoptosis and increased the expression of *Bcl-2* protein and declined the expression of *Bax* protein. A recent report also showed that ligustrazine protects rat renal tubular cell apoptosis induced by gentamicin (Juan et al., 2007). Therefore, ligustrazine effectively reverses cisplatin-induced renal tubular toxicity and this may be related to the inhibition of renal tubular cell apoptosis.Along with previous reports, our study showed that ligustrazine may play a renoprotective role on cisplatin-induced renal tubular toxicity. It is interesting to know that ligustrazine may have certain degrees of anti-tumor effect. It has been reported that ligustrazine inhibited the proliferation of human small cell lung cancer H446 cells and gastric cancer cells (Zhang et al., 1999, 2003a,b). It also enhances the anti-tumor effect of chemotherapy drugs through direct inhibition of tumor cells and immune regulation (Wang and Chen, 2003).

In conclusion, the results of the present study indicate that cisplatin generated renal tubular toxicity by inducing the formation of reactive oxygen species and apoptosis. Ligustrazine dose-dependently protects the kidney tissues against cisplatin insult. Thus, ligustrazine may play a renoprotective role on cisplatin-induced renal tubular toxicity through its antioxidant properties and by suppressing apoptosis. This study provides persuasive evidence for ligustrazine as a therapeutic strategy in cisplatin-induced renal tubular toxicity.

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