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Effect of levosimendan, a calcium sensitizer, on cisplatin-induced nephrotoxicity in rats

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ABSTRACT

We investigated the effect of levosimendan on cisplatin (Cis)-induced nephrotoxicity. Rats were divided into four groups (n = 6). The first and second groups received normal saline (control) and intraperitoneal (i.p.) cisplatin (6 mg/kg) on day 7, respectively. The third and fourth groups received a single intraperitoneal (i.p.) injection of Cis on day 7 and levosimendan (1 mg/kg/day, orally) or vehicle for 10 days, respectively. At day 11, animals were anaesthetized and blood collected and kidneys removed. Another four groups were treated the same as the previous four groups to measure renal blood flow. Cis induced nephrotoxicity as evidenced by biochemical, histopathological and hemodynamic changes. Levosimendan partially reduced Cis-induced increase in plasma urea, creatinine and neutrophil gelatinase-associated lipocalin (NGAL) levels and decrease in creatinine clearance. Levosimendan partially reduced Cis-induced increase in urinary albumin/creatinine ratio, N-Acetyl-β-D-Glucosaminidase (NAG) and kidney Injury Molecule-1 (KIM-1). Levosimendan significantly attenuated the effect of Cis on plasma concentration of plasma tumor necrosis factor–alpha (TNF-α), antioxidant indices [catalase and superoxide dismutase (SOD)] and lipid peroxidation. Cis induced acute tubular necrosis with tubular dilatation, interstitial edema and congestion. Levosimendan attenuated the remarkable renal damage and reduced renal blood flow induced by Cis. In conclusion this study shows that levosimendan has a partial protective effect on Cis-induced nephrotoxicity. The protective effect of levosimendan is shown to be related to its anti-inflammatory, antioxidant and vasodilator effects.

1. Introduction

Levosimendan is a positive inotropic agent with vasodilating properties [1]. Levosimendan exerts its positive inotropic effect by increasing the sensitivity of troponin C to calcium in myocardial cells. At higher doses, the drug also acts as a phosphodiesterase III inhibitor. It also activates adenosine triphosphate (ATP)-sensitive potassium channels in mitochondria protecting myocardial and potentially other cell types against ischemia reperfusion injury and perhaps other insults [2]. In addition, it also causes vasodilatation by opening the ATP-sensitive potassium channels in smooth muscle cells [3]. In addition to its inotropic and vasodilator effects, levosimendan has several other important actions, including anti-inflammatory and anti-apoptotic effects [4,5].

Levosimendan is currently indicated for the treatment of chronic heart failure [6]. Levosimendan has been shown to protect the kidneys from ischemia/reperfusion injury in rabbits and pigs [7,8], renal dysfunction caused by endotoxemia in mice [9] and renal glomerular and tubular damage in Dahl/Rapp salt sensitive rats [10]. In addition, levosimendan demonstrated a renoprotective effect in patients with acute decompensated heart failure and in patients with heart transplantation [11,12].

Cisplatin [Cis, cis-diamminedichlorolatinum (II)]-based combination therapy regimens are used in the treatment of many types of cancer but the chief factor limiting its use is nephrotoxicity [13]. The pathology of Cis-induced acute kidney injury is complex and consists of inflammation, vascular injury, oxidative stress, and proximal tubular injury [14].

The aim of the present study was to examine the effect of levosimendan, on kidney structure and function and renal hemodynamics in cisplatin-induced nephrotoxicity, and to elucidate further the possible mechanisms of action of these effects.

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2. Materials and methods

2.1. Animals

Male Sprague Dawley (SD) rats were obtained from the small animal house, Sultan Qaboos University and housed in a room at a temperature of 22 ± 2 °C, relative humidity of about 60%, with a 12 h light–dark cycle (lights on at 6:00), and fed standard diet and tap water. All experimental designs were approved by the Medical Research Committee, College of Medicine and Health Sciences, Sultan Qaboos University. All procedures involving animals and their care were carried out in accordance with the guidelines of the Animal Ethical Committee of Sultan Qaboos University and international laws and policies (EEC Council directives 2010/63/EU, 22 September 2010 and NIH Guide for the Care and Use of Laboratory Animals, NIH Publications, 8th edition, 2011).

2.2. Biochemical and histopathological studies

2.2.1. Experimental design

Male Sprague Dawley (SD) rats (n = 24) were randomly distributed into four equal groups and treated as follows:

Group 1: Control; received saline injection intraperitoneally (i.p.), single dose on day seven.

Group 2: Cisplatin; received cisplatin (6 mg/kg, i.p.), single dose on day seven.

Group 3: Levosimendan; received levosimendan (1 mg/kg), by oral gavage for 10 consecutive days and saline on the seventh day of treatment.

Group 4: Cisplatin + levosimendan: received levosimendan (1 mg/kg), by oral gavage for 10 consecutive days and cisplatin (6 mg/kg, i.p.) on the seventh day of treatment.

Doses of cisplatin was selected according to previously published work [15]. We also choose the dose of levosimendan (1 mg/kg) as this dose reduced renal glomerular and tubular damage in Dahl/Rapp salt sensitive rats [10].

Rats were weighed at the beginning and end of the experiment. The animals were placed in metabolic cages one day before sacrifice, and the amount of urine voided during the 24 h was measured. Collected urine was stored deep frozen (−80 °C) after its volume had been recorded.

2.2.2. Biochemical measurements

Blood was collected from the abdominal aorta of each animal and centrifuged at 4 °C to separate plasma. The plasma collected was frozen at −80 °C pending analysis. Kidneys were removed, weighed and a small portion of the upper part of the right kidney was excised and placed in formalin for subsequent histopathology. The remainder of the right kidney and the left kidney were individually wrapped in aluminum foil and then dipped in liquid nitrogen and stored at a temperature of −80 C, pending analysis. Homogenization of kidney was done in cold PBS buffer by ULTRA-TURRAX homogenizer in ice. After this, homogenate was centrifuged for 10 min in a micro centrifuge, at 5000 rpm and temperature at 4 °C and supernatant was collected for analysis.

Plasma urea and creatinine as well as urine creatinine and albumin were measured using fully automated chemistry analyzer BS-120, MINDRAY, Shenzhen Mindray Bio-Medical Electronics Co (Shenzhen, China). Plasma tumor necrosis factor–alpha (TNF-α) was measured by ELISA kit (Life Technologies Corp., Frederick, MD, USA) and neutrophil gelatinase-associated lipocalin (NGAL) by ELISA kit (Thermo Scientific, Frederick, MD, USA). Renal catalase, superoxide dismutase (SOD) and malondialdhyde were measured by a colorimetric assay kit (BioVision, Milpitas, CA, USA). Urinary N-Acetyl-β-D-Glucosaminidase (NAG) was measured by colorimetric Assay Kit (Diazyme, Poway, USA) and Kidney Injury Molecule-1 (KIM-1) by ELISA kit (R & D Systems, Minneapolis, MN, USA)

2.2.3. Histopathological examination

The renal tissues from all groups were fixed in 10% neutral-buffered formalin, dehydrated in increasing concentrations of ethanol, cleared with xylene and embedded in paraffin and 5 μm sections were prepared from kidney paraffin blocks and stained with hematoxylin and eosin. The microscopic scoring of the kidney sections was carried out in a blinded fashion by a pathologist who was unaware of the treatment groups.

2.3. Hemodynamic study

Another 24 rats were divided into 4 groups (350–550 g). Same experimental protocol as for biochemical and histopathological studies was performed. Renal blood flow was measured as previously reported [16,17]. The rats were anaesthetized with ketamine (75 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). PE_{50} cannulae, filled with heparinized normal saline (25 IU/ml in 0.9% NaCl), were inserted into the right carotid artery for the measurement of mean arterial pressure by a pressure transducer (TSD104 A, Biopac Systems, Santa Barbara, California, USA). An ultrasonic probe (1 RB, Hughes Sacks Electronik-Harvard Apparatus, March-Hugstetten, Germany) was placed around the left renal artery to measure renal blood flow and was connected to a flow meter (Hughes Sacks Electronik-Harvard Apparatus, March-Hugstetten, Germany). After a 10-15 min stabilization period, baseline renal blood flow were monitored on a data acquisition system (MP 150, Biopac Systems, Santa Barbara, California, USA).

2.4. Chemicals

Cisplatin was provided from Mylan S.A.S., (Saint-Priest, France) and levosimendan from Sigma-Aldrich, (St. Louis, MO, USA).

2.5. Statistical analysis

Data were expressed as means ± SEM, and were analyzed with GraphPad Prism Version 5.03 for Windows software (Graphpad Software Inc., San Diego, USA). Comparisons between the groups were performed by one way analysis of variance ANOVA, followed by Bonferroni comparisons or Unpaired *T* test whenever appropriate. *P* values < 0.05 were considered significant.

3. Results

3.1. Effect of levosimendan on physiological parameters in Cis induced nephrotoxicity in rats

Table 1 shows that Cis significantly reduced body weight gain and water intake and increased urine output but did not have a significant effect on relative kidney weight when compared with the control group. Levosimendan alone did not significantly affect any of the above parameters. Levosimendan significantly increased water intake in Cis treated rats but did not affect other parameters.

3.2. Effect of levosimendan on biochemical parameters in Cis induced nephrotoxicity in rats

Fig. 1 shows that there was an increase in plasma creatinine (+823% and +510%), urea (+516% and +389%) and a decrease in creatinine clearance (−97% and −92%) in Cis and Cis + levosimendan groups, respectively when compared with control. Levosimendan significantly decreased plasma creatinine (−33%) and urea (−25%) and increased creatinine clearance (+164%) in Cis treated rats compared to Cis only treated rats. Levosimendan alone did not significantly affect any of the above parameters.

Fig. 2 shows that there was a significant reduction in renal SOD (-41% and -28%) and catalase (-55% and -25%) activities in Cis and

Table 1
Effect of treatment with levosimendan (Lev) on some physiological parameters in rats with cisplatin (Cis)-induced nephrotoxicity in rats.

Parameters/ Treatment	Control	Cis	Lev	Cis + Lev
Initial body weight (g)	305.17 ± 2.68	305 ± 1.81	305.17 ± 2.09	305 ± 1.65
Final body weight (g)	346.33 ± 3.43	308 ± 4.23[a]	351 ± 3.17[b]	315.17 ± 5[a,c]
Change in body weight (%)	13.51 ± 1.12	0.97 ± 0.91[a]	15.04 ± 1.18[b]	3.34 ± 1.63[a,c]
Relative kidney weight (%)	0.74 ± 0.03	0.81 ± 0.03	0.73 ± 0.03	0.78 ± 0.02
Water intake (mL/24 h)	27.08 ± 1.36	15.42 ± 1.50[a]	24.58 ± 1.00[b]	22.08 ± 2.08[b]
Urine output (mL/24 h)	8.00 ± 1.03	19.50 ± 1.02[a]	8.17 ± 0.48[b]	17.50 ± 1.23[a,c]

Values in the table are means ± SEM (n = 6).
Lev (1 mg/kg) was given to rats daily by oral gavage for 10 days. On the 7th day of treatment, a single dose of Cis (6 mg/kg) was administered intraperitoneally to induce ARF. On the 10th day, the rats were placed in metabolic cages to collect urine.
Relative kidney weight $= \frac{\text{kidney weight}}{\text{Body weight}}$ X 100.
Different superscripts indicate significance as follows ($P < 0.05$ was considered significant):
[a] vs. Control.
[b] vs. Cis.
[c] vs. Lev.

Cis + levosimendan groups, respectively when compared with control. There was a significant increase in malondialdhyde (+27%) level in Cis-treated group but not in Cis + levosimendan treated group when compared with control. Levosimendan significantly increased renal SOD (+21%) and catalase (+65%) activities and decreased MDA (−17%) levels in Cis treated compared to Cis only treated rats. Levosimendan alone did not significantly affect any of the above parameters.

Fig. 3 shows that there was an increase in urinary KIM-1 (+126% and +69%), NAG (+177% and +82%) levels or activities and UACR (+2565% and +757%) in Cis and Cis + levosimendan groups, respectively when compared with control. Levosimendan significantly decreased urinary KIM-1 (−25%), NAG (-34%) levels or activities and UACR (-68%) in Cis treated rats compared to Cis only treated rats. Levosimendan alone did not significantly affect any of the above parameters except it increased KIM-1 levels (+27%) when compared to control group.

Fig. 4 shows that there was a significant increase in plasma TNF-α (+156% and +112%) and NGAL (+442% and +266%) concentrations in Cis and Cis + levosimendan groups, respectively when compared with control. Levosimendan significantly decreased plasma TNF-α (−17%) and NGAL (−32%) in Cis treated rats compared to Cis only treated rats. Levosimendan alone did not significantly affect any of the above parameters.

3.3. Histopathology

Examination of kidney specimens from the control group showed normal glomeruli and tubules (Fig. 5A). Examination of renal slices from rats treated with Cis alone showed acute tubular necrosis with tubular dilatation, interstitial edema and congestion (Fig. 5B). Sections from levosimendan (1 mg/kg/day)-treated rats showed small foci of tubular necrosis with regeneration activity (Fig. 5C). Sections from levosimendan (1 mg/kg/day) with Cis-treated rats showed near normal tubules and glomeruli (Fig. 5D).

3.4. Hemodynamic study

Fig. 6 shows that there was a significant reduction in renal blood flow (-70%) in Cis treated group compared to control group. There was no significant changes in renal blood flow in Cis + levosimendan group compared to control group. Levosimendan significantly increased renal blood flow (+155%) in Cis treated group compared to Cis only treated rats. Levosimendan alone did not significantly affect renal blood flow.

4. Discussion

Cis is used in the treatment of many types of cancer, however patients experience many side effects such as nausea and vomiting, myelosuppression, neurotoxicity, ototoxicity and nephrotoxicity that limit its use [18]. Clinical studies showed decreased estimated glomerular filtration rates and increased urinary albumin excretion and serum creatinine following a cisplatin dose in 8–40% of patients within 10 days [19]. In this study, Cis induced acute renal failure in rats as confirmed by reduced body weight gain and polyuria when compared to control rats. In addition Cis significantly increased plasma urea, creatinine, urinary albumin/creatinine ratio and reduced creatinine clearance. Cis- induced nephrotoxicity was associated with renal tubular injury as shown by increased markers of renal tubular injury such as plasma NGAL and urinary NAG and KIM-1. Cis induced nephrotoxicity was also associated with an inflammatory process as shown by increased inflammatory cytokines (TNF-α). In addition, Cis induced oxidative stress as shown by reduced renal SOD and catalase activities and increased MDA concentrations. Histopathologically, Cis caused remarkable renal damage when compared with control. Our results on Cis-induced nephrotoxicity are in accordance with the results of many previous studies in rats [17,20]. Moreover, in this study Cis-induced reduction in renal blood flow is in agreement with previous reports [16]. Cis-induced kidney injury is associated with increased kidney vascular resistance and histological damage to proximal tubular cells resulting in decreased blood flow and ischemic injury of the kidneys, contributing to a decline in glomerular filtration rate [21].

In the present study, Levosimendan partially attenuated Cis induced nephrotoxicity as evidenced by decreased plasma urea, creatinine and NGAL concentrations and urinary albumin/creatinine ratio, NAG and KIM-1 concentrations and increased creatinine clearance. Levosimendan partially attenuated also the histopathological changes induced by Cis. This protective effect may be due to reduced Cis-induced inflammation as evidenced by reduced plasma TNF-α. In addition, levosimendan reduced oxidative stress as evidenced by increased renal SOD and catalase activities and reduced MDA. Levosimendan was shown to possess anti-inflammatory activity against acute phases of inflammation. The possible mechanism of anti-inflammatory action involves reduction in the TNF-α, IL-1 and IL-6 levels and oxidative stress [22]. The renal anti-oxidative properties of levosimendan have also been shown previously in rats [23]. Furthermore, levosimendan reversed the reduction in renal blood flow induced by Cis. Previous reports have shown that treatment with levosimendan has been shown to protect the kidneys from ischemia and reperfusion injury induced by renal artery clamping in anesthetized pigs and in rabbits by preventing oxidative stress and apoptosis [7,8]. Mitochondrial K(ATP) channels and NO-related mechanisms were shown to be involved in the protective effect of levosimendan [8]. In addition, levosimendan was shown to protect mice from experimental renal dysfunction caused by endotoxemia [9]. Furthermore, levosimendan treatment for seven weeks

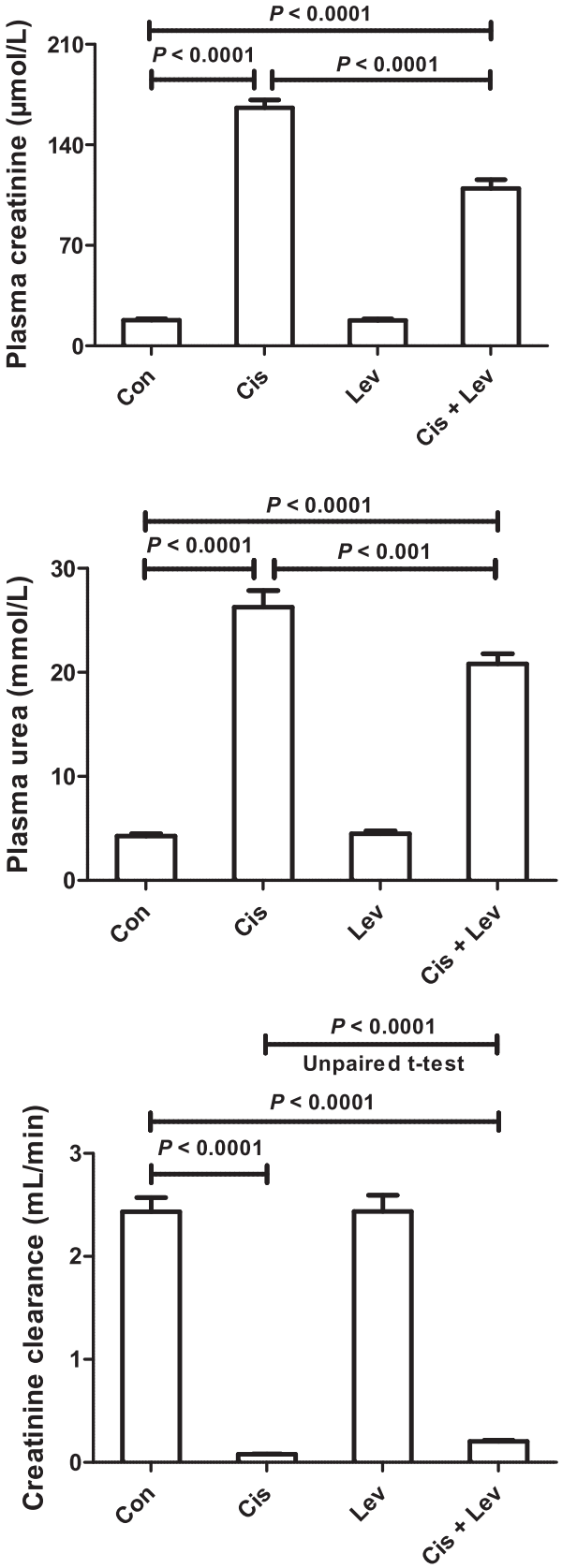

Fig. 1. The plasma concentration of creatinine and urea and creatinine clearance in control rats, rats treated with cisplatin (Cis), or levosimendan (Lev), separately or in combination. Each column and vertical bar represents mean ± SEM (n = 6).

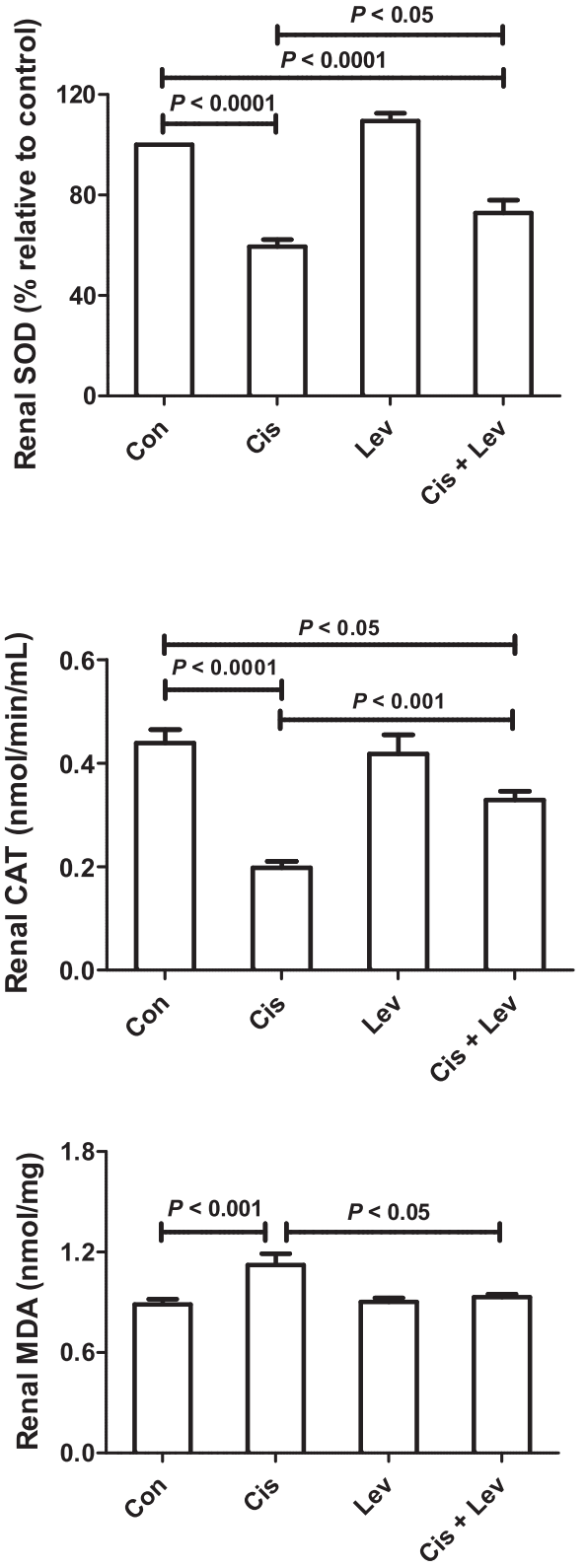

Fig. 2. The renal concentration or activity of superoxide dismutase (SOD), catalase (CAT) and malondialdhyde (MDA) in control rats, rats treated with cisplatin (Cis), or levosimendan (Lev), separately or in combination. Each column and vertical bar represents mean ± SEM (n = 6).

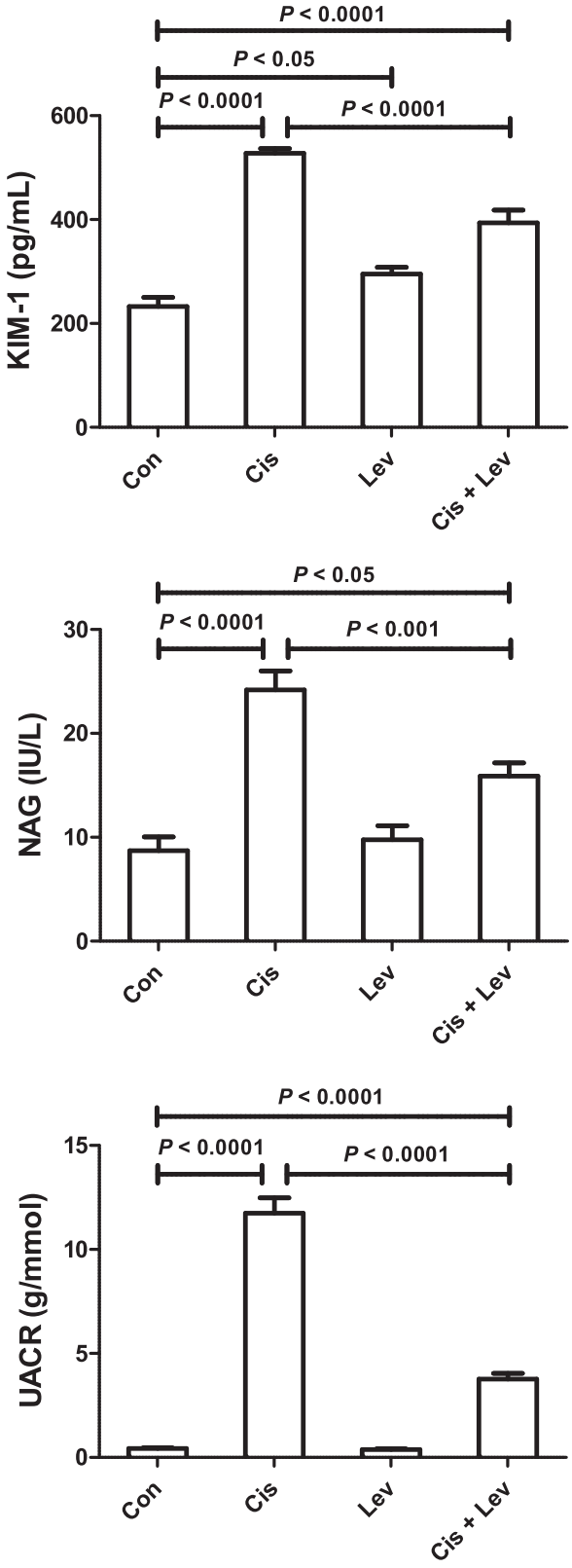

Fig. 3. The urinary concentration or activity of kidney Injury Molecule-1 (KIM-1), N-Acetyl-β-D-Glucosaminidase (NAG) and albumin/creatinine ratio in control rats, rats treated with cisplatin (Cis), or levosimendan (Lev), separately or in combination. Each column and vertical bar represents mean ± SEM (n = 6).

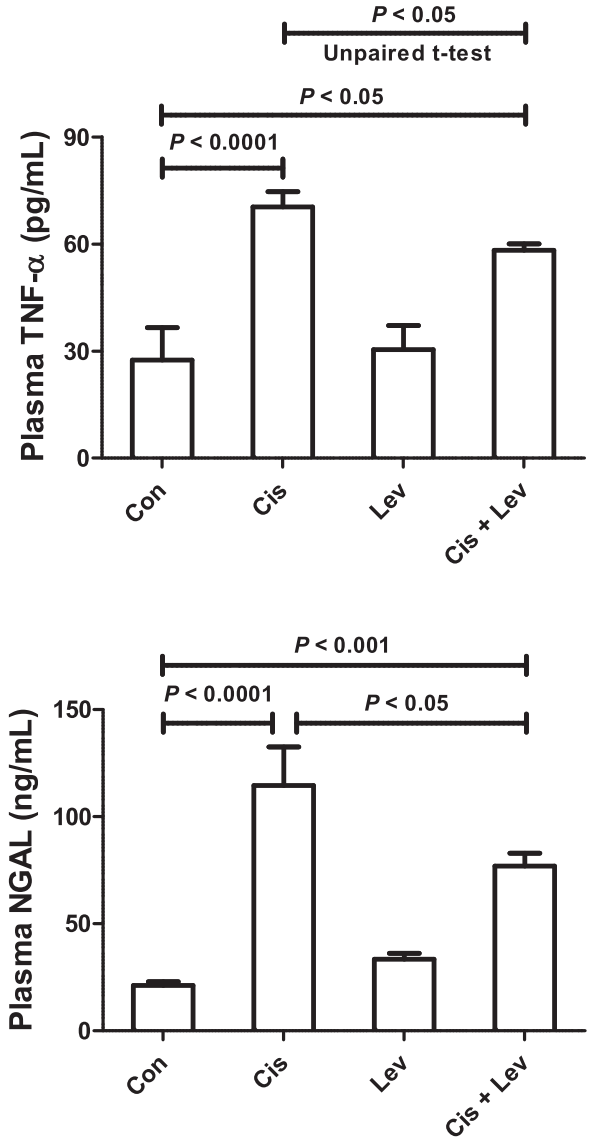

Fig. 4. The plasma concentration of tumor necrosis factor (TNF-α) and neutrophil gelatinase-associated lipocalin (NGAL) in control rats, rats treated with cisplatin (Cis), or levosimendan (Lev), separately or in combination. Each column and vertical bar represents mean ± SEM (n = 6).

attenuated renal glomerular and tubular damage in Dahl/Rapp salt sensitive rats [10]. The renoprotective effects of levosimendan were previously demonstrated in patients with acute decompensated heart failure and in patients with heart transplantation [11,12]. Fedele et al. [11] summarized the different proposed renoprotective mechanisms of levosimendan as (a) increase in renal blood flow due to haemodynamic improvement; (b) increased renal perfusion via vasodilation through K_{ATP} channel opening; (iii) reversal of angiotensin-II-mediated mesangial cell contraction with a consequent increase in glomerular filtration rate and (iv) anti-inflammatory and antiapoptotic effects. In the present study there were small foci of tubular necrosis with regeneration activity in the levosimendan group and increased in urinary KIM-1 levels. However levosimendan alone did not have a significant effect on renal function (plasma urea and creatinine and creatinine clearance) and other markers of renal injury (NAG, NGAL and UACR). The significance of these small foci of tubular necrosis is not quite clear. Pagel et al. [24] showed mild renal toxicity of levosimendan (50 mg/kg) and only after 13 weeks.

In conclusion, the present study demonstrates that levosimendan attenuated Cis-induced nephrotoxicity possibly through its anti-inflammatory, antioxidant and vasodilator effects. Other mechanisms including antiapoptic effects, hemodynamic improvement and blockade

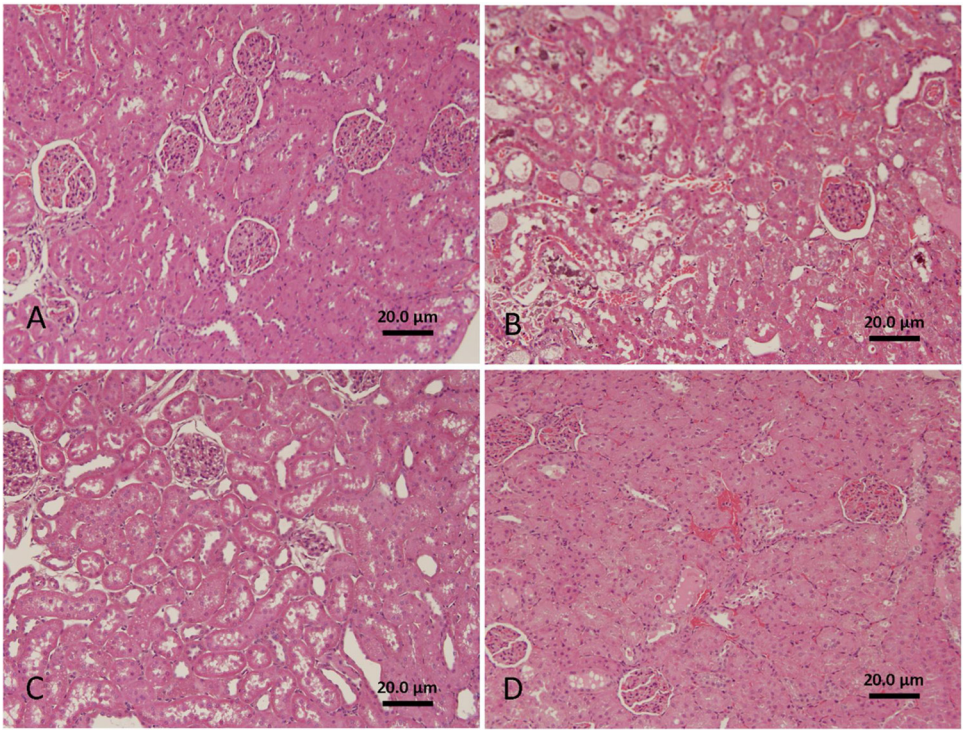

Fig. 5. Histopathologic pictures of the kidneys from (A), Normal control showing normal glomeruli and tubules, (B) animals treated with cisplatin (6 mg/kg) showing acute tubular necrosis with tubular dilatation, interstitial edema and congestion, (C), animals treated with levosimendan (1 mg/kg/day) showing small foci of tubular necrosis with regeneration activity, (D) animals treated with cisplatin (6 mg/kg) plus levosimendan (1 mg/kg/day) showing near normal tubules and glomeruli.

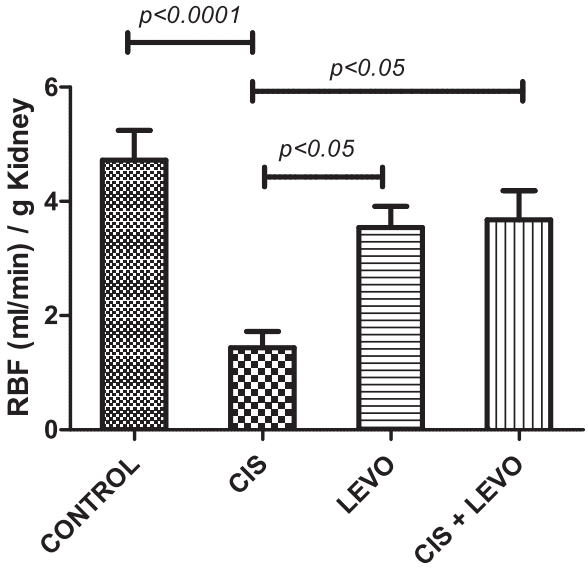

Fig. 6. Renal blood flow (ml/min/g) in control rats, rats treated with cisplatin (Cis), or levosimendan (Lev), separately or in combination. Each column and vertical bar represents mean ± SEM (n = 5–6).

of angiotensin II effects on glomeruli may also be involved. Future experimental and clinical studies are warranted to establish the renoprotective effect of levosimendan in acute and chronic renal failure.

Conflict of interest

The authors reported no conflict of interests regarding the publication of this article.

Transparency document

The Transparency document associated with this article can be found in the online version.

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References

[1] P. Pollesello, Z. Papp, J.G. Papp, Calcium sensitizers: what have we learned over the last 25 years? Int. J. Cardiol. 203 (2016) 543–548.
[2] D. Farmakis, J. Alvarez, T.B. Gal, D. Brito, F. Fedele, C. Fonseca, A.C. Gordon, I. Gotsman, E. Grossini, F. Guarracino, V.P. Harjola, Y. Hellman, L. Heunks, V. Ivancan, A. Karavidas, M. Kivikko, V. Lomivorotov, D. Longrois, J. Masip, M. Metra, A. Morelli, M. Nikolaou, Z. Papp, A. Parkhomenko, G. Poelzl, P. Pollesello, H.B. Ravn, S. Rex, H. Riha, S.E. Ricksten, R.H.G. Schwinger, B. Vrtovec, M.B. Yilmaz, M. Zielinska, J. Parissis, Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: an expert panel position paper, Int. J. Cardiol. 222 (2016) 303–312.
[3] I. Gödény, P. Pollesello, I. Edes, Z. Papp, Z. Bagi, Levosimendan and its metabolite OR-1896 elicit K_{ATP} channel-dependent dilation in resistance arteries in vivo, Pharmacol. Rep. 65 (2013) 1304–1310.
[4] J.T. Parissis, S. Adamopoulos, C. Antoniades, G. Kostakis, A. Rigas, S. Kyrzopoulos, E. Iliodromitis, D. Kremastinos, Effects of levosimendan on circulating proinflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure, Am. J. Cardiol. 93 (2004) 1309–1312.
[5] K.A. Krychtiuk, L. Watzke, C. Kaun, E. Buchberger, R. Hofer-Warbinek, S. Demyanets, J. Pisoni, S.P. Kastl, S. Rauscher, M. Gröger, A. Aliabadi, A. Zuckermann, G. Maurer, R. de Martin, K. Huber, J. Wojta, W.S. Speidl, Levosimendan exerts anti-inflammatory effects on cardiac myocytes and endothelial cells in vitro, Thromb. Haemost. 113 (2015) 350–362.
[6] B. Gong, Z. Li, P.C. Yat Wong, Levosimendan treatment for heart failure: a systematic review and meta-analysis, J. Cardiothorac. Vasc. Anesth. 29 (2015) 1415–1425.
[7] N. Yakut, H. Yasa, B. Bahriye Lafci, R. Ortac, E. Tulukoglu, M. Aksun, C. Ozbek, A. Gurbuz, The influence of levosimendan and iloprost on renal ischemia-reperfusion: an experimental study, Interact. Cardiovasc. Thorac. Surg. 7 (2008) 235–239.
[8] E. Grossini, C. Molinari, P. Pollesello, G. Bellomo, G. Valente, D. Mary, G. Vacca, P. Caimmi, Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs, J. Pharmacol. Exp. Ther. 342 (2012) 376–388.
[9] R.A. Zager, A.C. Johnson, S. Lund, S.Y. Hanson, C.K. Abrass, Levosimendan protects against experimental endotoxemic acute renal failure, Am. J. Physiol. Renal Physiol. 290 (2006) F1453–F1462.
[10] A. Biala, P. Finckenberg, A. Korpi, M. Loytainen, E. Martonen, J. Levijoki, E. Mervaala, Cardiovascular effects of the combination of levosimendan and valsartan in hypertensive Dahl/Rapp rats, J. Physiol. Pharmacol. 62 (2011) 275–285.
[11] F. Fedele, N. Bruno, B. Brasolin, C. Caira, A. D'Ambrosi, M. Mancone, Levosimendan improves renal function in acute decompensated heart failure: possible underlying

mechanisms, Eur. J. Heart Fail. 16 (2014) 281–288.
[12] I. Knezevic, G. Poglajen, E. Hrovat, A. Oman, T. Pintar, J.C. Wu, B. Vrtovec, Haddad F The effects of levosimendan on renal function early after heart transplantation: results from a pilot randomized trial, Clin. Transplant. 28 (2014) 1105–1111.
[13] B.H. Ali, M.S. Al Moundhri, Agents ameliorating or augmenting the nephrotoxicity of cisplatin and other platinum compounds: a review of some recent research, Food Chem. Toxicol. 44 (2006) 1173–1183.
[14] C.N. Sharp, L.J. Siskind, Developing better mouse models to study cisplatin-induced kidney injury, Am. J. Physiol. Renal Physiol. 313 (2017) F835–F841.
[15] B.H. Ali, S. Al-Salam, M. Al Za'abi, K.A. Al Balushi, A.S. AlMahruqi, S. Beegam, I. Al-Lawatia, M.I. Waly, A. Nemmar, Renoprotective effects of gamma-aminobutyric acid on cisplatin-induced acute renal injury in rats, Basic Clin. Pharmacol. Toxicol. 116 (2015) 62–68.
[16] A.M. Abdelrahman, S. Al Salam, A.S. AlMahruqi, I.S. Al-Husseni, M.A. Mansour, B.H. Ali, N-acetylcysteine improves renal hemodynamics in rats with cisplatin-induced nephrotoxicity, J. Appl. Toxicol. 30 (2010) 15–21.
[17] Y.M. Al Suleimani, A.M. Abdelrahman, A.S. AlMahruqi, I.S. Al-Husseni, M.H. Tageldin, M.E. Mansour, B.H. Ali, Interaction of nimesulide, a cycloxygenase-2 inhibitor, with cisplatin in normotensive and spontaneously hypertensive rats, Food Chem. Toxicol. 48 (2010) 139–144.
[18] R. Purena, R. Seth, R. Bhatt, Protective role of Emblica officinalis hydro-ethanolic leaf extract in cisplatin induced nephrotoxicity in rats, Toxicol. Rep. 5 (2018) 270–277.
[19] A. Atilano-Roque, X. Wen, L.M. Aleksunes, M.S. Joy, Nrf2 activators as potential modulators of injury in human kidney cell, Toxicol. Rep. 3 (2016) 153–159.
[20] B.H. Ali, A.M. Abdelrahman, S. Al-Salam, M. Sudhadevi, A.S. AlMahruqi, I.S. Al-Husseni, S. Beegam, S. Dhanasekaran, A. Nemmar, M. Al-Moundhri, The effect of sildenafil on cisplatin nephrotoxicity in rats, Basic Clin. Pharmacol. Toxicol. 109 (2011) 300–308.
[21] S. Hajian, M. Rafieian-Kopaei, H. Nasri, Renoprotective effects of antioxidants against cisplatin nephrotoxicity, J. Nephropharmacol. 3 (2014) 39–42.
[22] E. Karakus, Z. Halici, A. Albayrak, Y. Bayir, A. Aydin, D. Unal, E. Cadirci, I. Ferah, E. Odaci, Beneficial pharmacological effects of levosimendan on antioxidant status of acute inflammation induced in paw of rat: involvement in inflammatory mediators, Basic Clin. Pharmacol. Toxicol. 112 (2013) 156–163.
[23] I. Gecit, S. Kavak, M.B. Yüksel, H. Basel, H. Bektas, H.A. Gümrükçüoglu, I. Meral, H. Demir, Effect of short-term treatment with levosimendan on oxidative stress in renal tissues of rats, Toxicol. Ind. Health 30 (2014) 47–51.
[24] P.S. Pagel, P.J. Pentikainen, M.-L. Toivonen, M.S. Nieminen, L. Lehtone, J.G. Papp, D.C. Warltier, Pharmacology of levosimendan: a new myofilament calcium sensitizer, Cardiovasc. Drugs Rev. 14 (1996) 286–316.