

CISPLATIN NEPHROTOXICITY

PhD thesis

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1. INTRODUCTION

In our Time lung cancer incidence increase. With new drugs the treatments possibilities are higher and with this the side effects of chemotherapy also increase. High-dose Cisplatin (Cp) – based combination chemotherapy regimens are used as front-line treatments of small cell (SCLC) and non small cell lung cancer (NSCLC). The therapeutic effects of Cp are significantly improved by dose escalation, but in this time the nephrotoxicity is also escalated. The modality to prevent this now is only hydration. Different hydration protocols were developed, but one certain effective it isn't. The medical studies showed, that age, female sex, smoking decreased the Cp-induced renal function damage. They are no data about influence of comorbidities as, for example, hypertension (HT), ischemic heart disease (CD) and diabetes mellitus (DM). Our patients are older, with this they comorbidities incidence increased. This can have influence for Cp-induced nephrotoxicity. This patients could have nephrosclerosis sooner they serum creatinin level [creat] increased.

Vitamin E and C, selen, melatonin, erythropoietin, amifostine, etc. can protect kidneys from Cp nephrotoxicity in animals. Amifostine, with approbation from Food and Drug Administration (FDA) to prevent Cp nephrotoxicity, is not used for expensiveness. CV 247 (CV) is composed of manganese and cupper gluconates, sodium salicylate and ascorbic acid, which components are known in animal experiences Cp nephrotoxicities preventive substance, could have nephroprotective effect.

2. OBJECTIVES

1. Could pre- Cp [creat] predict Cp nephrotoxicity?
2. Can predict calculated isotopic GFR before Cp treatment the Cp-induced nephrotoxicity?
3. Have influence the patient's comorbidities for incidence of Cp nephrotoxicity?
4. Is CV protective against Cp nephrotoxicity?

3. METHODS

3.1. Prospective clinical study

The Pulmo-Oncology Unit of Dept. of Pulmonology at Semmelweis University (Budapest, Hungary) treats 250-300 nonsmall and small cell lung cancer patients annually. Since Cp-induced reversible or persistent uraemia was estimated to occur in 30% of our patients, in order to investigate whether GFR was already reduced before Cp treatment when [creat] was still normal, in prospective study, we measured GFR by clearance of ^{99m}Tc -DTPA- diethylene thiamine pentaacetic acid- (Izotóp Intézet Kft, Budapest, Hungary) in 38 stage IIIB-IV lung cancer patients with normal [creat] scheduled for Cp-based chemotherapy. ^{99m}Tc -DTPA clearance was measured after administration of 40 MBq i.v. at the Dept. of Radiology- and Oncotherapy of Semmelweis University by L. Duffek. Patients were then grouped according to their highest post-Cp [creat] either below (n=15) or above (n=23) the upper limit of the reference range ($>106 \mu\text{mol}\cdot\text{L}^{-1}$) any time during their chemotherapy (2-4 cycles). Cp was administrated at $75\text{mg}\cdot\text{m}^{-2}$ i.v. (Teva Hungary, Budapest) in each cycle. Cp infusions were ≥ 21 days part.

3.2. Retrospective clinical study

We retrospectively analysed records of patients (n=242) suffering from stage IIIA-IV nonsmall or small cell lung cancer and receiving chemotherapy between January and December 2006. Based on initial evaluation of the 242 patients, three major subgroups were formed according the absence or presence of the comorbidities CD and/or DMIH. The NC subgroup had no hypertension, ischemic heart disease or

diabetes mellitus. The CD subgroup was formed based on presence of long-term, medically controlled hypertension and ischaemic heart disease (together cardiovascular disease; n=110), and the DMIH subgroup was based on the combined presence of diabetes mellitus and ischaemic heart disease without hypertension (n=52). The diagnosis of chronic arterial hypertension was based on history and the use of antihypertensive medications. Ischaemic heart disease was diagnosed based on history, ECG abnormalities and previous treatment with coronary vasodilators, platelet aggregation inhibitors or percutaneous transluminal coronary angioplasty. None of the CD patients suffered from uncontrolled hypertension, angina pectoris, acute myocardial infarction or cardiac decompensation, or from any other acute or severe cardiovascular comorbidity that could have contraindicated chemotherapy with high-dose Cp. Diabetes mellitus was diagnosed based on history, treatment with insulin (n=5) or oral antidiabetic treatment (n=47) and higher than normal fasting serum glucose concentration. None of the DMIH patients suffered from uncontrolled hyperglycaemia or had symptoms of major complications of diabetes. Urinary protein test showed opalescence ($\geq 1 \text{ g}\cdot\text{day}^{-1}$) in two patients and slight opalescence ($0.5\text{--}1.0 \text{ g}\cdot\text{day}^{-1}$) in two other patients; the majority had negative ($<0.5 \text{ g}\cdot\text{day}^{-1}$) results. Patients received several subsequent combined chemotherapy courses, always containing high-dose Cp ($75 \text{ mg}\cdot\text{m}^{-2} \text{ i.v.}$), and each pre- and the highest post-Cp [creat] concentration values were recorded. Cp-induced persistent uraemia (which indicates Cp nephrotoxicity) was a frequent cause of exclusion from further Cp treatment. The number of these patients was compared between the three groups. Clinical data, such as age, sex, chronic comorbidity, blood pressure and stage of lung cancer were collected. With regard to laboratory data, serum glucose and [creat] concentrations were analysed. [creat] was determined based on the modified Jaffe two-point kinetic reaction using commercially available test from Dialab (Wiener Neudorf, Austria). C_{creat} (eGFR) was calculated according the Cockcroft–Gault equation. This calculation was selected because the mean age of our patients was <65 yers.

Cp was provided by Teva Hungary (Budapest, Hungary) and EBEWE Pharma (Unterach, Austria) and administered at a dose of $75 \text{ mg}\cdot\text{m}^{-2}$. One of three additional chemotherapeutic agents was given in combination with Cp: gemcitabine (gem, $1,250 \text{ mg}\cdot\text{m}^{-2}$; Eli Lilly, Houten, the Netherlands), etoposide (etop, $3\times 120 \text{ mg}\cdot\text{m}^{-2}$) and

paclitaxel (pac, 175 mg·m⁻²; both Bristol-Myers Squibb, Princeton, NJ, USA). Neutropenia was treated with granulocyte colony-stimulating factor (filgrastim, 48 mU; Amgen, Breda, the Netherlands), severe thrombocytopenia with platelet transfusion, and anaemia with erythropoietin (Epoetin alfa, 40,000 IU·week⁻¹; Janssen-Cilag, Centocor, Leiden, the Netherlands) and/or transfusion as indicated. Patients received antinociceptive and antiemetic drugs, bisphosphonate, methylprednisolone and other symptom relievers, as needed.

An *i.v.* infusion of 500 mL 0.9% NaCl was followed by either gemcitabine, taxol or etoposide in a further 500 mL saline. After a third 500-mL saline infusion, Cp was infused again in 500 mL. In our hands, infusion of 500 mL usually takes 20–30 min. Following Cp, the fifth 500 mL saline was infused (total volume of saline 2.500 mL within ~2.5 h) and the infusion treatment was ended with 100 mL 20% mannitol (Baxter, Deerfield, IL, USA) *i.v.*

Data are presented as means±SEM. Statistical analysis was performed using GraphPad software (Graph Pad Prism 5.0; Graph Pad Software, Inc., San Diego, CA, USA) using Fisher's exact test, the Chi-squared test and t-tests (paired and unpaired) as appropriate. One-or two-way ANOVA and the Kruskal–Wallis test was used to compared more than two groups. Normally distributed data were analysed by ANOVA and non-Gaussian distributed or nonparametric values were analysed by Kruskal–Wallis test. After one-way ANOVA, if significant difference ($p<0.05$) was found, the Newman–Keuls multiple comparison *post hoc* test was used for further analysis. After two-way ANOVA, a Bonferroni post-test was used. After the Kruskal–Wallis test, Dunn's multiple comparison *post hoc* test was performed. The applied tests are described in the table and figure legends.

3.3. Animal experience

The study was conducted on 40 male, 8-week old Wistar rats weighing 175–190 g. The animals were randomly divided into 4 groups (n=10/group). They were kept individually under standard conventional conditions according to European Council Directive 123. The study conformed to the Declaration of Helsinki guidelines and was approved by the local Animal Ethic Committee. Cp (10 mg in 20 ml) was obtained from TEVA, Israel. The composition of CV247 (Pharmaserve Ltd, Manchester UK) was the

following: 40 mg ascorbic acid, 2 mg manganese gluconate (unique selling proposition-USP), 2 mg copper gluconate and 35 mg sodium salicylate per millilitre solution. The dose given was $2 \times 120 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ vitamin C (Vit. C), $2 \times 10^5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ sodium salicylate, $2 \times 6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ copper gluconate and $2.6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ manganese gluconate. Methyl cellulose mucilage (Dow Chemicals, Midland, MI, USA) was prepared in distilled water (1 %).

Control group (C) received 1% methyl cellulose at $10 \text{ ml}\cdot\text{kg}^{-1}$ body weight⁻¹, per oral (p.o.) by gastric gavage twice daily for 14 days. Another group of rats received CV247 at $3 \text{ ml}\cdot\text{kg}^{-1}$ body weight⁻¹, p.o. twice daily for 14 days (CV). Two groups were intraperitoneally injected with a single dose of Cp at $6.5 \text{ mg}\cdot\text{kg}^{-1}$ body weight⁻¹. Cp was suspended in $10 \text{ ml}\cdot\text{kg}^{-1}$ 1% methyl cellulose. One of the groups injected with Cp was subsequently treated with vehicle (C) or CV at $3 \text{ ml}\cdot\text{kg}^{-1}$ body weight⁻¹, p.o. twice daily for 14 days (CV+Cp). All rats were weighed and food and water consumptions were also measured daily. On day 12 were 1.5 ml blood samples taken from all rats by retro-orbital puncture under isoflurane anaesthesia after a 20-hour food deprivation. The blood was anticoagulated with citrate and centrifuged twice at $2500 \text{ r}\cdot\text{min}^{-1}$ for 10 min at +4 C to obtain plasma. (creat) and blood urea nitrogen (BUN) were determined from the plasma by colorimetric tests using commercially available kits. Rats were terminally anaesthetised with an overdose of pentobarbital on day 14. Blood was collected by aortic puncture and one kidney from each animal was removed and weighed. Kidneys were fixed in 8% buffered formalin (pH 7.4), paraffin sections were prepared and stained with haematoxylin–eosin. Renal histological changes were blindly evaluated using a 5-grade severity scale (0 =no change; 1= minimal changes; 2=mild changes; 3=moderate changes; 4=severe changes). The cyclooxygenase-2 (COX-2) immunohistochemistry was done using a mouse monoclonal COX-2 primary antibody (Novocastra, UK) at 1:100 dilution. The secondary antibody was a peroxidase-conjugated mouse/rabbit polymer (Dako Real™ Envision™ /HRP, Rabbit/Mouse). Diaminobenzidine was used for visualisation.

Means±SD are given throughout. The statistical comparisons were performed by two-way repeated measures ANOVA with Bonferroni post hoc test or Mann-Whitney U test using GraphPad Prism 5 for Windows, or by two-way ANOVA using

the SPSS 17 for Windows, when appropriate. The level of significance was set at $p < 0.05$.

4. RESULTS

4.1. Clinical studies results

4.1.1. Results of prospective clinical study

Out of the 38 lung cancer patients, 23 patients responded with pathologically increased [creat] after Cp (table I), although pre-treatment [creat] values were normal in both groups. Pre-treatment GFR, as measured by clearance of ^{99m}Tc -DPTA, was significantly reduced by ~25% in those lung cancer patients with azotaemia who responded to 2-4 cycles of Cp treatment.

Table I. Pre-Cp glomerular filtration rate (GFR) of 38 initially non uraemic lung cancer patients

Subgroup	pre-Cp [creat]	post-Cp [creat]	pre-Cp GFR (mL·min ⁻¹ ·m ⁻²)	Age (yrs)	Males/ females
	(μmol.L ⁻¹)				
Cp nephrot. (n=23)	79±4 ^{*1}	167±12 ^{*1}	73.51±4 ^{*1}	63.6±1.5 ^{ns1}	13/10 ^{ns2}
No Cp nephrot. (n=15)	68±3	87±4	98.6±4.6	60.5±2.8	8/7

*: $p < 0.05$, not significant (ns): $p > 0.05$ compared with „No Cp nephrotoxicity” group;

1: unpaired t-test; 2: Fischer’s exact test

4.1.2. Results of retrospective clinical study

Table II contain all patient’s clinical data and in table III we can see patients [creat] values before and after Cp treatments.

Table II. Clinical data of patients receiving high-dose Cp for lung cancer

	NC(n=80)	CD (n=110)	DMIH(n=52)
Age (yrs)	56±1	60±1*	62±1*
Males/females (n)	45/35	66/44 ^{ns}	33/19 ^{ns}
BMI (kg·m ⁻²)	24.3±0.4	25.4±0.4 ^{ns}	25.4±0.6 ^{ns}
Dose of Cp per treatment (mg)	123±2	126±2 ^{ns}	124±4 ^{ns}
Total dose of Cp (mg)	375±22	399±22 ^{ns}	392±43 ^{ns}
Mean number of cycles (n)	3.1±0.2	3.2±0.2 ^{ns}	3.2±0.3 ^{ns}
Cp+gem/etop/tax(patients number)	38/41/1	52/55/3 ^{ns}	25/24/3 ^{ns}
Systolic/diastolic blood pressure (mmHg)	132±2/81±1	134±2/81±1 ^{ns}	137±3/84±2 ^{ns}
Cardiac frequency beats (beats ·min ⁻¹)	81±1	82±1 ^{ns}	86±2 ^{ns}

*: p<0.05, ns: p>0.05 compared with NC

Table III.[creat] in lung cancer patients receiving 1-4 cycles of high-dose Cp

Cp cycle		NC	Cd	DMIH
1st	Patients number	80	110	52
	[creat] $\mu\text{mol}\cdot\text{L}^{-1}$			
	Pre-Cp	77 \pm 1	78 \pm 1 ^{ns}	77 \pm 3 ^{ns}
	Post-Cp	82 \pm 2*	95 \pm 4*†	94 \pm 4*†
2nd	Patients number	68	96	49
	[creat] $\mu\text{mol}\cdot\text{L}^{-1}$			
	Pre-Cp	80 \pm 2	86 \pm 2 ^{ns}	82 \pm 3 ^{ns}
	Post-Cp	88 \pm 4*	105 \pm 5*†	110 \pm 6*†
3rd	Patients number	42	64	31
	[creat] $\mu\text{mol}\cdot\text{L}^{-1}$			
	Pre-Cp	85 \pm 3	91 \pm 3 ^{ns}	83 \pm 4 ^{ns}
	Post-Cp	91 \pm 5*	113 \pm 5*†	117 \pm 9*†
4th	Patients number	35	47	30
	[creat] $\mu\text{mol}\cdot\text{L}^{-1}$			
	Pre-Cp	84 \pm 4	95 \pm 3 ^{ns}	89 \pm 3 ^{ns}
	Post-Cp	93 \pm 5*	117 \pm 8*†	121 \pm 5*†

*: $p < 0.05$ compared with pre-Cp (paired t-test); not significant (ns): $p > 0.05$;

†: $p < 0.05$ compared with NC (two-way ANOVA with Bonferroni after test).

Pre- treatments [creat] are not increased. After every treatment [creat] increased significant, what shows Cp nephrotoxicity. In NC group [creat] was every time physiologic, but in other two groups were increased. Before the new cycles of chemotherapy [creat] level decreased in normal range, these need to continue Cp therapy. DMIH patients' kidney pre- treatments were not intact, that is responsible for this high number of post-Cp azotaemia. Table III. shows, that this comorbidities predispose patients to Cp nephrotoxicity. They incidence can't predict by pre treatment [creat] values.

Cp induced azotaemia was in NC group 7.5, in CD group 20.9 ($p < 0.05$ compared with NC) and in DMIH group 30.8% ($p < 0.01$ compared with NC) (Figure 1.)

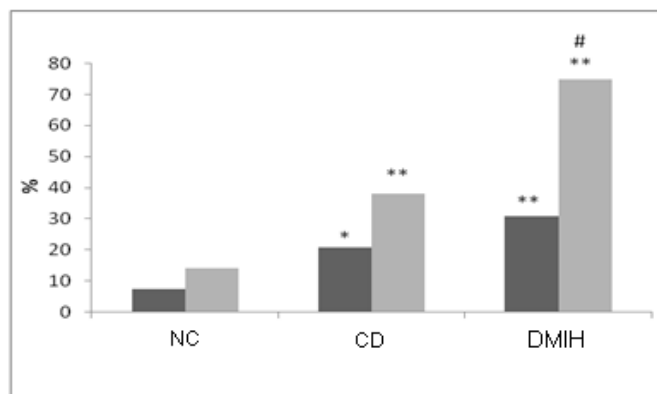


Figure 1. Frequency of nephrotoxicity (dark) and nephrotoxicity-related drop-out from further Cp treatment (bright) in lung cancer patients receiving 1-4 cycles of high-dose Cp and suffering from hypertension and ischaemic heart disease (CD), or diabetes mellitus and ischaemic heart disease (DMIH), or being free from these severe comorbidities (NC).

*: $p < 0.05$ compared with NC, **: $p < 0.01$ compared with NC; #: $p < 0.01$ compared with CD (two-tailed difference tests).

Calculated GFR before Cp treatments were significantly higher in that group, which later don't have azotaemia. That shows, calculated GFR could be predictive for Cp nephrotoxicity. This reproduces table I. results.

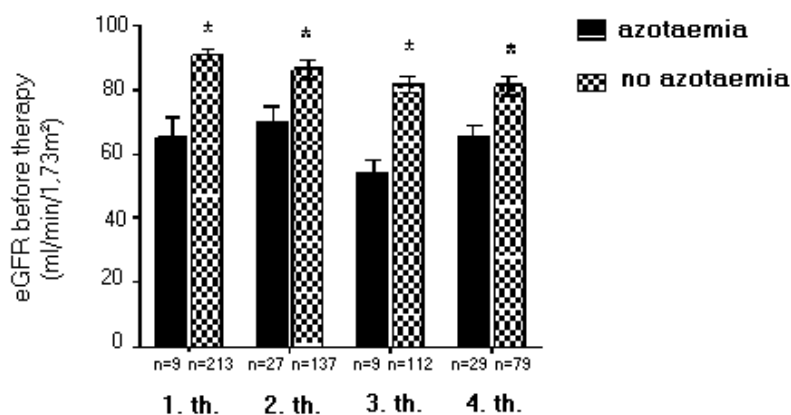


Figure 2. Summary of pre-Cp treatment calculated GFR values together in 3 patients groups (NC, CD, DMIH)

Difference was calculated with Mann Whitney test. *: $p < 0.01$ Cp related azotaemia with no azotaemia.

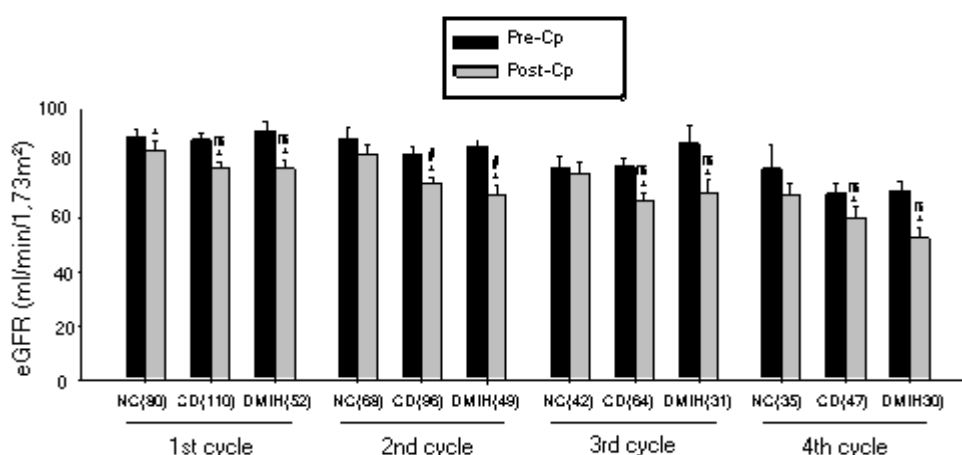


Figure 3. Pre- (dark) and post- (bright) Cp estimated glomerular filtration rate (eGFR) values during the 1st-4th cycles of high-dose Cp treatments in lung cancer patients suffering from no comorbidity (NC), controlled hypertension and ischaemic heart disease (CD), or controlled diabetes mellitus and ischemic heart disease (DMIH).

Numbers above the bars represent the number of patients. *:p<0.05 compared with pre-Cp (paired t-test); not significant (ns) compared with NC (two-way ANOVA with Bonferroni after test); #:p<0.05 compared with NC (two-way ANOVA with Bonferroni after test).

When the estimated glomerular filtration rate (eGFR) before Cp therapy was lower or between 60-70 mL·min⁻¹·m⁻², the incidence of post-Cp nephrotoxicity was very high.

4.2. Animal experience

4.2.1. Body weight

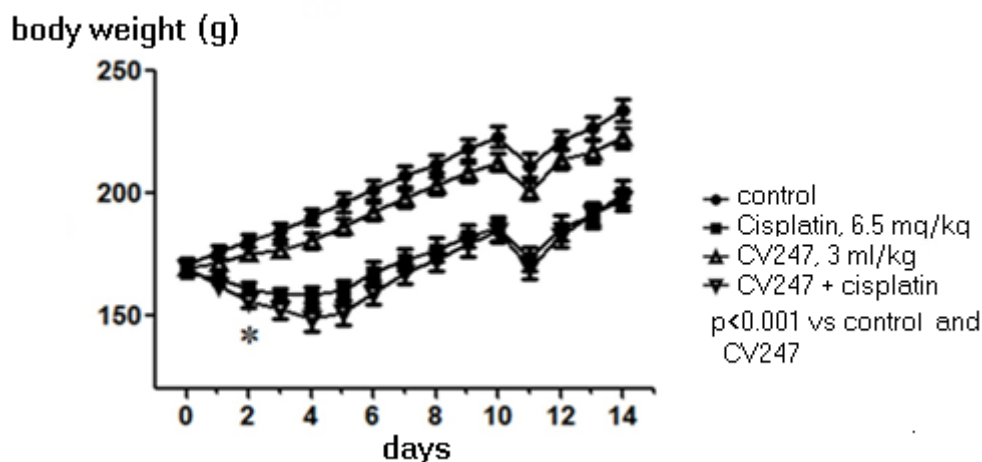


Figure 4. Cp decreased significant body weight of rats from 2nd day.

Body weight of rats steadily increased in control group from 171 ± 8 g to 234 ± 15 g over a study period of 14 days with a drop on day 11 after the overnight food deprivation before blood sampling. In comparison with baseline values, Cp caused a 5.5% peak body weight loss ($p < 0.001$) on day 3 after treatment. CV treatment did not influenced body weight in comparison with C and Cp groups.

4.2.2. Water consumption

CV consistently increased water consumption in comparison with C group (Figure 5) which was statistically significant on days 8, 9 and 11 ($p < 0.05$ all). Cp caused short, non-significant decrease in water consumption on day 2 after its administration (daily -5- -10 mL). Therefore, from day 4, rats in Cp and CV+Cp groups drank significantly more water than rats in group C. Co-administration of CV to Cp did not alter water consumption in comparison with the group treated with Cp only. In comparison with C group animals with Cp consume more water. CV alone increased water consumption.

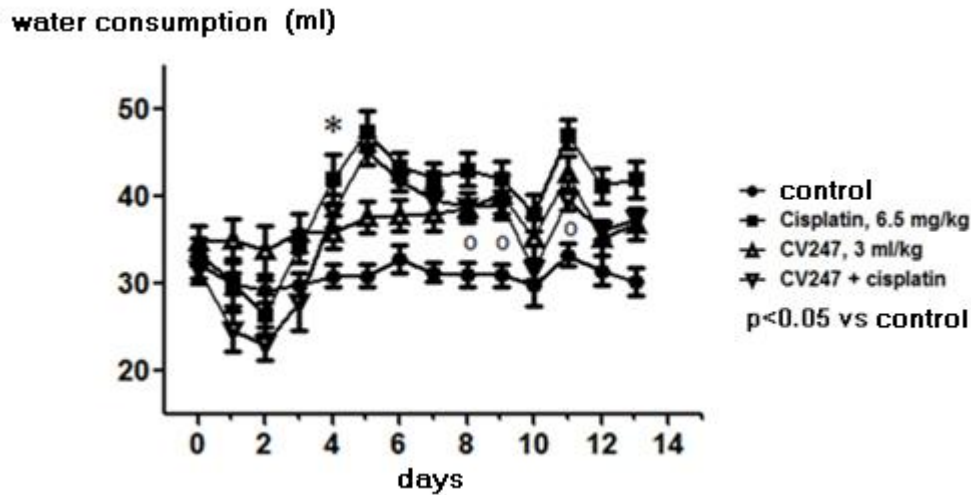


Figure 5. From 5 day (*) water consumption was significantly increased in groups treated with Cp and CV+Cp in comparison to the C group. The open circles show that on days 8, 9 and 11 water consumption was significantly increased in the group treated with CV in comparison to the group treated with vehicle.

The statistical analysis was performed by two-way ANOVA with Bonferroni after test.

4.2.3. Renal function

[creat] and [BUN] values were within physiological limit in groups C and CV. ([creat]: 17.0- 22.5 $\mu\text{mol}\cdot\text{L}^{-1}$, [BUN]: 6.63- 10.48 $\text{mmol}\cdot\text{L}^{-1}$). Cp increased both significant ($p < 0.01$) in day 12 taked blood samples. CV did not alter ($p > 0.05$ both) these effects of Cp on renal function (Figure 6 and 7).

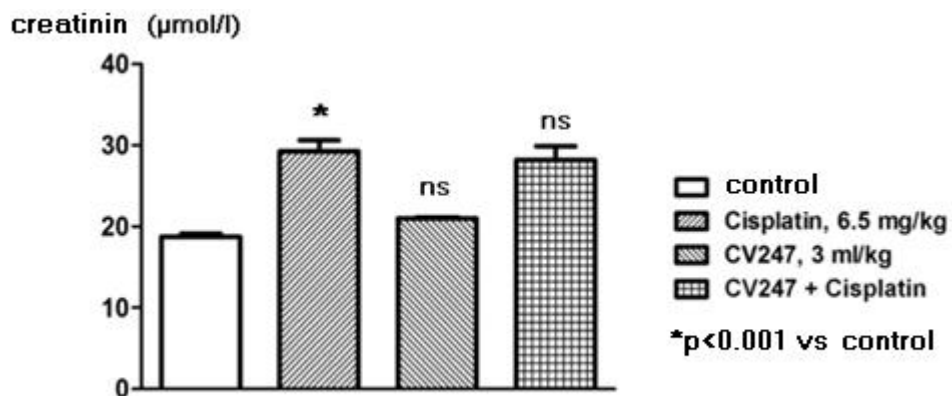


Figure 6. CV did not alter Cp caused azotaemia. (two-way ANOVA)

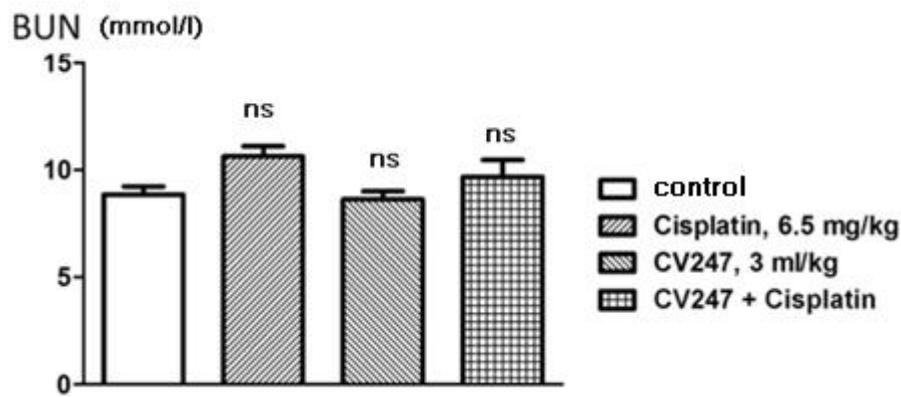


Figure 7. CV have no effect of [BUN]. (two-way ANOVA)

4.2.4. Kidney histology and immunohistochemistry

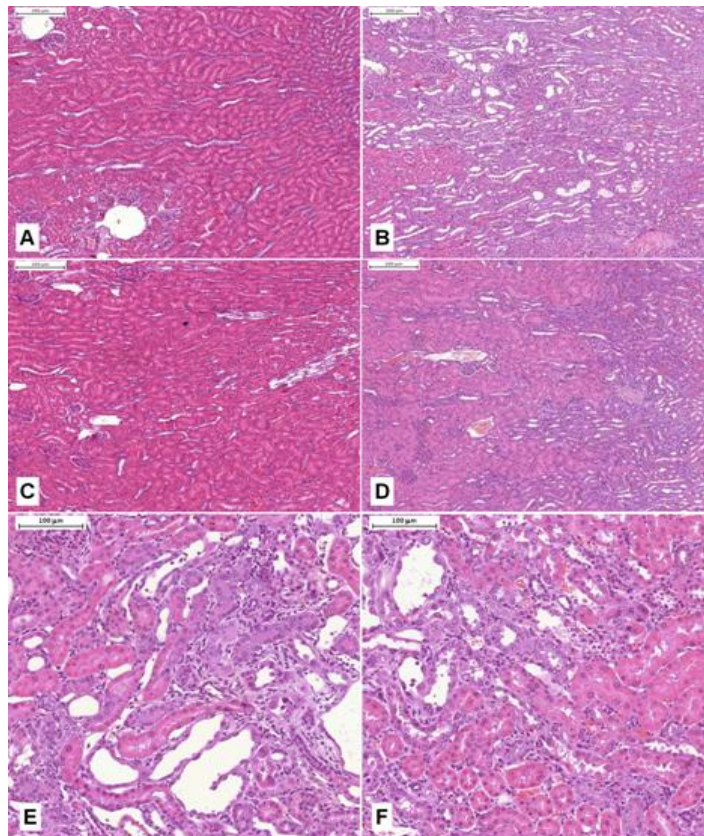


Figure 8. CV have nephroprotective effect. (haematoxylin-eosin staining).

A.C:normal histology; B+E.Cp:severe degree of tubulointerstitial abnormality (3.67 ± 0.50); C.CV: normal histology; D+F.CV+Cp: significantly less severe alterations we in group Cp (2.67 ± 0.71 ; $p < 0.01$) E and F higher magnification of sections. Abnormalities were statistifcally compared by two-way ANOVA.

No histological changes were seen in kidneys in groups C and CV; that show CV have no kidney nephrotoxicity. Blind assessment demonstrated a significant ($p<0.01$) reduction in the mean of histological kidney injury from 3.67 ± 0.50 in Cp to 2.67 ± 0.71 in CV+Cp group.

Immunohistochemistry related a moderate degree of focal COX-2 activity in the cytoplasm of tubular epithelium in the interstitial space and in the walls of major blood vessels (C: $1,20\pm0.42$, CV: $1,0\pm0,0$). Blind assessment of COX-2 immunoreactivity markedly increased in the groups treated with Cp and CV+Cp. Treatment with CV did not alter COX-2 immunoreactivity in comparison C but slightly (Cp: 3.00 ± 0.71 versus CV+Cp: 2.44 ± 0.53 , $p=0.097$). Our study showed that CV could prevent Cp nephrotoxicity.

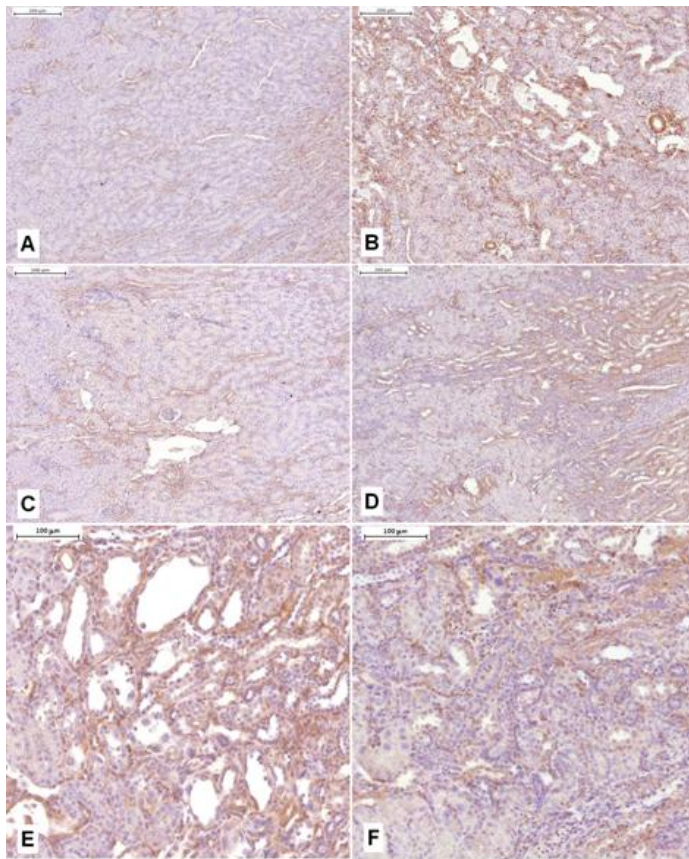


Figure 9. Cp effect and CV protective effect on COX-2 immunohistochemistry in renal cortex.

A.C: mild activity in the interstitium and tubular epithelium; B+E. Cp increased COX-2 activity in the damaged areas of the kidney (3.67 ± 0.50); C.CV: mild activity in the interstitium and tubular epithelium; D+F. CV+Cp: Cp effect is significantly decreased by

CV (2.67 ± 0.71 ; $p < 0.01$) E and F higher magnification of sections. Abnormalities were statistically compared by Mann Whitney test.

5. CONCLUSIONS

- 1.The risk of nephrotoxicity should always be evaluated based on eGFR.
- 2.Lower eGFR (60-80 ml·perc⁻¹) with normal [creat] and [BUN] before Cp therapies predict Cp nephrotoxicity.
- 3.Coexisting CD or DMIH, because narrow the tolerance of the kidneys to Cp, increased the incidence of Cp nephrotoxicity.
4. CV 247 can attenuate Cp caused nephrotoxicity.

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