English summary

Cisplatin (cis-diaminedichloroplatinum II, CDDP) is an antitumor agent which is widely used with a broad spectrum of activity in human cancers. However, its clinical use is limited by the onset of a severe dose-limiting nephrotoxicity. Regarding the mechanisms of nephrotoxicity of cisplatin, so far several hypotheses have been put forward, among which oxidative stress is a noticeable one.

Many chemoprotectors have been evaluated to alleviate the severity of this toxic side-effect. In recent years, different types of antioxidant interventions have been reported, one of them included the renin angiotensin system inhibition therapy.

Captopril, is an angiotensin converting enzyme inhibitor, effectively used as antihypertensive agent: It contains a free SH-group, and is suggested to ameliorate chemically-induced nephrotoxicity.

Losartan, is an angiotensin II receptor blocker, clinically used as antihypertensive, and is reported to prevent oxidative stress. This suggests the promising role of losartan as angiotensin II receptor blocker in treatment of cisplatin-induced nephrotoxicity.

The present study is an experimental trial to assess the nephrotoxic effect of cisplatin as well as the nephroprotective potential of either captopril or losartan. Another goal of this study, is to investigate the possible protective mechanism(s) by which ACE inhibitor (captopril) or angiotensin receptor blocker (losartan) counteract cisplatin-induced nephrotoxicity.

In view of the previously mentioned results, the following could be concluded:

- Cisplatin administration produces severe nephrotoxicity in rats, where oxidative stress plays an important role as evidenced by increased kidney content of lipid peroxides and depletion of GSH (although not apparent in-vivo).

- The present study clearly demonstrates that captopril and losartan could be promising drugs for clinical use as nephroprotectors against cisplatin-induced nephrotoxicity. Furthermore, this study sheds light on the mechanisms involved in their nephroprotective effect. They ameliorated the kidney injury induced by cisplatin and guard against oxidative stress by restoring cellular defense mechanism, through increasing the kidney GSH content and reducing lipid peroxidation. In addition, the nephroprotective activity of captopril is most likely attributed to its structure as a sulfur-containing nucleophile.

- It should be mentioned that the nephroprotective abilities of captopril or losartan were not mediated through lowering platinum uptake by the kidney tissue.

- Captopril and losartan are equipotent in their nephroprotective potential. Since the two drugs are used clinically this may simplify their introduction as protective agents.

- Further investigations are clearly warranted to establish the clinical applicability of these drugs in patients with kidney diseases especially those associated with cisplatin administration, and to explore the possible interference of these drugs with the antitumor activity of cisplatin.