Effects of Sacubitril/Valsartan on Cisplatin Induced Nephrotoxicity in Mice	
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SUMMARY. Nephrotoxicity is a serious health concern associated with cisplatin chemotherapy in cancer treatment. Various studies have shown that the renin-angiotensin system (RAS) is involved in the pathogenesis of several renal disorders. However, the results of earlier studies evaluating the effect of RAS inhibitors on cisplatin-induced nephrotoxicity are conflicting. Sacubitril/valsartan (Sac/Val) is a combination drug for heart failure that contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan. In this work, the effects of Sac/Val on cisplatin-induced nephrotoxicity in mice were evaluated. Nephrotoxicity was determined by analysing kidney function, oxidative stress, inflammation, and renal damage parameters. Cisplatin (25 mg/kg, i.p.) increased the kidney index, serum and urinary levels of various nephrotoxic biomarkers, including pro-inflammatory cytokines. Additionally, cisplatin elevated renal production of malondialdehyde (MDA), proinflammatory cytokines and chemokines while lowering the level of antioxidant enzymes (glutathione, super-oxide dismutase and catalase) and anti-inflammatory cytokine, IL-10. Administration of Sac/Val (60 mg/kg, p.o.) markedly reduced all serum and urinary markers of nephrotoxicity elevated by cisplatin. Additionally, Sac/Val significantly reduced elevated levels of MDA, pro-inflammatory cytokines and chemokines, and prevented a decrease in IL-10 and antioxidant enzyme levels in kidney tissue. Sac/Val also reduced the histopathological changes caused by cisplatin in the proximal tubule. Our findings suggest that Sac/Val reduces cisplatin-induced kidney damage by suppressing the production of inflammatory mediators and oxidative stress. Therefore, Sac/Val could be a promising alternative candidate to ameliorate nephrotoxicity in patients receiving cisplatin chemotherapy.