International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2018.1046.1050

Short Communication
Effects of Candesartan and Losartan on Thioacetamide Induced Low Grade Renal Dysfunction in Rats

[1,2]Hussam Aly Sayed Murad, [1]Misbahuddin Mohd Rafeeq and [3]Nader Nabil Malatani

[1]Department of Pharmacology, Faculty of Medicine, Rabigh campus, King Abdulaziz University, 21589, Jeddah, Saudi Arabia
[2]Department of Pharmacology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[3]Faculty of Medicine, Rabigh campus, King Abdulaziz University, 21589, Jeddah, Saudi Arabia

Abstract

Background and Objective: Equivocal evidence exists concerning the role of angiotensin receptor blockers (ARBs) in renal injury, whether they are reno-protective or reno-toxic. Effect of low and high dose of losartan and candesartan (ARBs) was evaluated on murine model of low grade renal dysfunction. **Materials and Methods:** Low grade renal dysfunction was induced by thioacetamide 50 mg kg^{-1} intraperitoneally once daily for two weeks. Rats were treated once daily by gastric gavage for 14 days as follows: Positive control (vehicle), two losartan (5 and 10 mg kg^{-1}) and two candesartan groups (0.1 and 0.3 mg kg^{-1}) and normal control group. At end of treatment, blood urea and creatinine were measured in addition to the histopathological examination of renal tissues. **Results:** Only losartan 10 mg kg^{-1} revealed significant decrease in blood urea and creatinine compared to the positive control group. Thioacetamide caused a decrease in glomerular cellularity, widening of capsular space and dilatation of tubular lumina with desquamation of epithelium. Only losartan 10 mg kg^{-1} reversed these changes. **Conclusion:** A high dose of losartan protects against low grade renal dysfunction in rats. Larger studies are recommended to further elucidate the underlying mechanisms.

Key words: Renal dysfunction, losartan, candesartan, low-grade and thioacetamide

Received: April 15, 2018 Accepted: August 13, 2018 Published: September 15, 2018

Citation: Hussam Aly Sayed Murad, Misbahuddin Mohd Rafeeq and Nader Nabil Malatani, 2018. Effects of candesartan and losartan on thioacetamide induced low grade renal dysfunction in rats. Int. J. Pharmacol., 14: 1046-1050.

Corresponding Author: Misbahuddin Mohd Rafeeq, Department of Pharmacology, Faculty of Medicine, Rabigh campus, King Abdulaziz University, 21589, Jeddah, Saudi Arabia Tel: 00966550309636

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Kidney is vital to maintain hemodynamics, salt and mineral homeostasis and excretion of toxic metabolites. It is more predisposed to toxicity due to high blood flow and its ability to concentrate the tubular fluid. Acute or chronic insult to kidneys may cause various types of renal dysfunction for example intraglomerular and tubular toxicity, diffuse inflammation, crystal nephropathy and thrombotic microangiopathy resulting in altered hemodynamics and retention of toxic metabolites[1]. It has also been suggested that generation of reactive oxygen species, by oxidation of polyunsaturated fatty acids in renal membrane lipids, with help of NADPH oxidase, contributes to renal damage[2]. In addition, there may be secondary involvement of other organs as a consequence to renal injury.

Thioacetamide (TAA) is a toxic compound classically used to induce hepatotoxicity of different grades including liver fibrosis, cirrhosis and neoplasm. The TAA has also been reported to induce a nephrotoxic model mimicking proximal tubule injury[3,4]. It may cause injury by free radical mediated lipid peroxidation and/or through its nephrotoxic metabolites. In addition, TAA metabolizes to acetate that is excreted through urine[5].

Angiotensin II is a proinflammatory mediator and is reported to play a significant role in renal inflammation by infiltration of macrophages. In addition, it increases the expression of other proinflammatory mediators like cellular adhesion molecules, different chemokines and various growth factors[6]. Hence, a protective and/or therapeutic role of angiotensin receptor blockers (ARBs) was speculated and several clinical and experimental studies were conducted in different models of renal damage.

It was reported that long term high dose of candesartan significantly reduced inflammation in rats with hypertensive renal damage mainly through nuclear factor (NF)-κB suppression[7] while the low dose failed. Another study in the rat obstructive uropathic model reported a preservation of renal mass and reduction of inflammatory mediators by candesartan[8]. Moreover, losartan has shown to protect against non-diabetic and non-hypertensive chronic kidney damage[9].

Nevertheless, some studies also reported a non-protection or even aggravation of renal injury by ARBs, for example losartan failed to protect against cisplatin induced renal damage[10]. Also, candesartan increased renal tissue damage in nitric oxide dependent salt sensitive rat hypertensive model[11]. The TAA is classically used to induce hepatic injury and ARBs have shown to protect against liver damage[12], but no study concerning the role of ARBs in low dose TAA-induced mild renal damage has been reported. Most of the studies have used high dose single TAA (300 mg kg^{-1}) to cause acute kidney damage. Thus, this study was designed to evaluate the role of two ARBs (losartan and candesartan) on mild low grade renal dysfunction which may mimic early diabetic or early hypertensive kidney disease.

MATERIALS AND METHODS

Induction of low grade renal dysfunction: Male rats (Sprague Dawley) weighing 120 -180 g were utilized in the present study. Rats were allowed to adapt to the laboratory conditions for one week before the initiation of experimentation. Rats were housed using plastic cages in a room at 22°C and 12:12 h light-dark cycle and were fed with standard chow diet and water *ad libitum*. The experimental procedure was approved by the research ethics committee and adhered to the international guidelines for use and care of laboratory animals. Induction of low grade renal dysfunction was done by injecting thioacetamide (TAA, 50 mg kg^{-1}) intraperitoneally once per day for two weeks[3]. The rats were randomly allocated into five different groups (n = 8) and treated once per day by gastric gavage for 14 days as follows: Positive control group (vehicle), two losartan groups (5 and 10 mg kg^{-1}) and two candesartan groups (0.1 and 0.3 mg kg^{-1}) in addition to the normal control group.

Serum measurements: At end of the treatment duration, blood samples were collected from orbital venous plexus in serum separator tubes under anesthesia by diethyl ether. After centrifugation (2500 rpm for 15 min) sera were collected and kept at -70°C for biochemical measurements. Serum urea and creatinine were measured by standard kits from Sigma-Aldrich (US).

Histopathological examination: After blood sampling, rats were dissected and kidney tissues were collected and fixed in 10% buffered formaldehyde. Kidney tissues were dehydrated with different ethanol solutions, embedded in paraffin and then cut into 3-5 µ thick sections. These sections were stained with hematoxylin and eosin and examined using a light microscope.

Statistical analysis: Data was expressed as Mean±SEM. The SPSS version 19 was used for statistical analysis. One-way ANOVA followed by Tukey's multiple comparison test was applied to evaluate the differences between groups. The $p<0.05$ was considered statistically significant.

RESULTS

Serum measurements: The urea and creatinine levels were elevated in the positive control group compared to the normal control group implying a successful induction model. Only losartan 10 mg kg^{-1}significantly reversed these elevations while other treatment groups showed non-significant changes (Table 1).

Histopathological examination: Low dose thioacetamide caused a decrease of the glomerular cellularity, widening of the capsular space and dilatation of the tubular lumina with desquamation of the lining epithelium shown in Fig. 1. Only losartan 10 mg kg^{-1} reversed these thioacetamide-induced changes while other treatments failed.

DISCUSSION

The present study found that losartan in a high dose range protects against mild renal injury. Biochemical parameters and histopathological changes were reversed by losartan 10 mg kg^{-1}. However, these findings could not be observed with either low dose losartan or any dose of candesartan. Protection in case of mild renal dysfunction by high dose losartan in this study implicates the significant role; a high dose of losartan can play in alleviating and reversing early stages of chronic systemic diseases affecting the kidney. In addition, a non-significant effect of candesartan may point towards a dose related and molecular class effect of losartan rather than generalized effect of ARBs[13].

Table 1: Levels of serum urea and creatinine after 14 days of treatment compared to the positive control group

Parameters	Normal control	Positive control	Losartan (5 mg kg^{-1})	Losartan (10 mg kg^{-1})	Candesartan (0.1 mg kg^{-1})	Candesartan (0.3 mg kg^{-1})
Urea (mmol L^{-1})	5.41±0.36	9.86±1.01	8.72±0.59	6.64±0.61*	8.58±1.27	9.21±0.59
Creatinine (μmol L^{-1})	34.01±3.61	50.33±4.16	43.61±2.31	36.21±3.03*	44.83±2.13	46.66±3.05

*p<0.05 vs. positive control

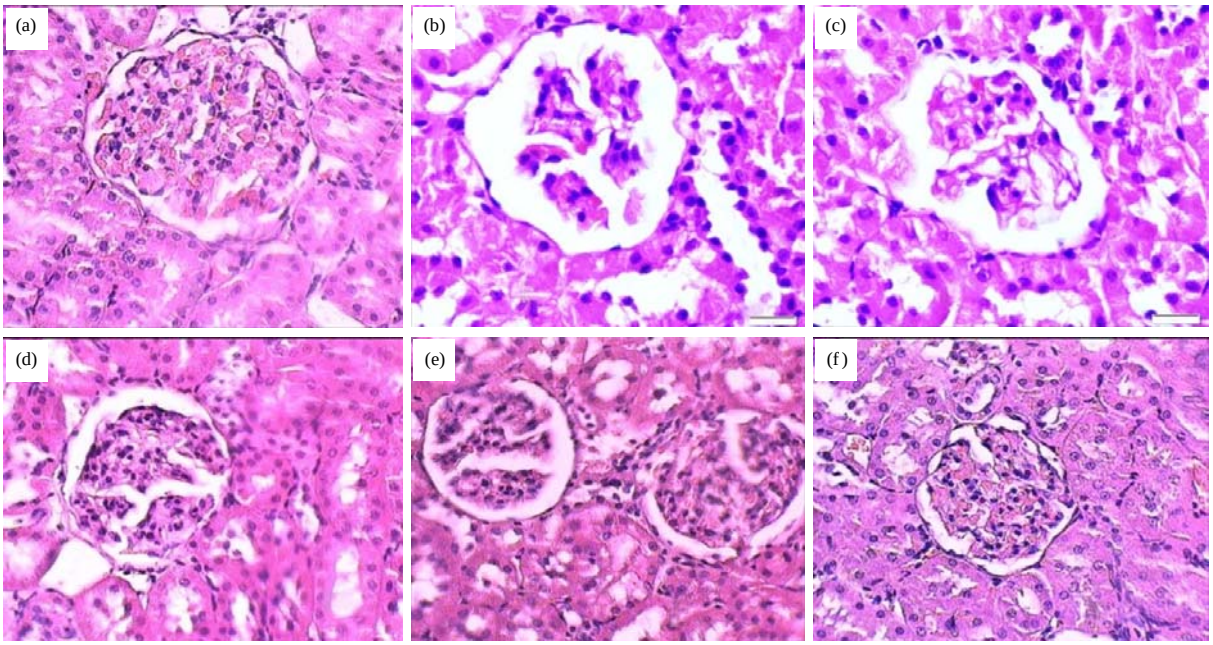

Fig. 1(a-f): Microscopic photographs of renal tissues in normal control, positive control and treated groups (a) Normal control group with intact renal structures, (b) Thioacetamide (positive control) group depicting a decrease of the glomerular cellularity, widening of the capsular space and dilatation of the tubular lumina with desquamation of the lining epithelium, (c) Candesartan 0.1 mg kg^{-1}, (d) Candesartan 0.3 mg kg^{-1}, (e) Losartan 5 mg kg^{-1} failed to reverse thioacetamide-induced changes and (f) Losartan 10 mg kg^{-1} showed a near normal capsular space with only slight lobulation of the glomerular tufts, good cellularity and normal tubular lumina

Equivocal results had been reported concerning the effect of ARBs on renal injury. These findings are in agreement with some previous studies[14-16] and in conflict with others[17-19]. Nevertheless, these studies have used different ARB agents in various dose ranges in different nephrotoxic models.

A study by Ripley and Hirsch[14] demonstrated protective effects of losartan in amyloidosis, different grades of diabetic and hypertensive nephropathy, glomerulosclerosis and other types of oxidative renal damage. However, losartan did not offer any protection against cisplatin, cyclosporine and gentamycin-induced nephrotoxicity in rats[18,19]. In another study candesartan offered potential benefit against progression of glomerulosclerosis and interstitial fibrosis in nephrectomized rats[17].

Candesartan also exhibited a dose-dependent protective effect on diabetic mice models. Low and intermediate doses decreased renal tubular damage and albuminuria, while high doses aggravated the inflammation, fibrosis and renal damage[20]. However, this effect was attributed to activation of other inflammatory and fibrotic pathways like mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase-1 (ERK1) and NFκB besides RAS and this may partially explain these findings of no protection. Moreover, another reason may be the difference in species and experimental model. Alternatively, the possible down-regulation of AT-2 but not AT-1 receptor may also partially explain the non-protection by candesartan, but this assumption needs further molecular studies[11]. Another aspect partially explaining the differences in response between losartan and candesartan is the difference in pharmacokinetics and structure activity relationships. It may be one of the reasons for losartan as a preferred choice in hypertensive patients with diabetes, hyperuricemia and compromised renal hemodynamic states[21].

CONCLUSION

Losartan in high doses protected against the mild renal damage induced by low dose thioacetamide while candesartan did not offer any benefit.

Limitations of the study are non-measurement of other inflammatory, oxidative and renal injury markers and non-inclusion of other members of ARBs. Further studies can be planned to generate a more scientific hypothesis.

SIGNIFICANCE STATEMENT

This study presents an important finding that losartan in a higher dose of 10 mg kg^{-1}, protects against mild renal dysfunction, often observed in early (or latent) stages of chronic diseases. Hence, it generates a crucial clinical hypothesis; whether high dose losartan can be considered in patients, reporting during early phase of disorders affecting the kidney.

ACKNOWLEDGMENT

The contribution of 5th year medical students Fares K. Bawareth, Youssef M. Ajaj, Mazen A. Alghamdi, Ammar O. Alminhali, Saud K. Althubaiti, Youssof O. Rayes, Abdulaziz Elsaedh, Mohammed Megaled is duly acknowledged.

REFERENCES

1. Schetz, M., J. Dasta, S. Goldstein and T. Golper, 2005. Drug-induced acute kidney injury. Curr. Opin. Crit. Care, 11: 555-565.
2. Etoh, T., T. Inoguchi, M. Kakimoto, N. Sonoda and K. Kobayashi *et al*., 2003. Increased expression of NAD(P)H oxidase subunits, NOX4 and p22phox, in the kidney of streptozotocin-induced diabetic rats and its reversibity by interventive insulin treatment. Diabetologia, 46: 1428-1437.
3. Barker, E.A. and E.A. Smuckler, 1974. Nonhepatic thioacetamide injury II. The morphologic features of proximal renal tubular injury. Am. J. Pathol., 74: 575-590.
4. Ferguson, M.A., V.S. Vaidya and J.V. Bonventre, 2008. Biomarkers of nephrotoxic acute kidney injury. Toxicology, 245: 182-193.
5. Chilakapati, J., M.C. Korrapati, R.A. Hill, A. Warbritton, J.R. Latendresse and H.M. Mehendale, 2007. Toxicokinetics and toxicity of thioacetamide sulfoxide: A metabolite of thioacetamide. Toxicology, 230: 105-116.
6. Brasier, A.R., A. Recinos and M.S. Eledrisi, 2002. Vascular inflammation and the renin-angiotensin system. Arterioscler. Thromb. Vasc. Biol., 22: 1257-1266.
7. Yu, C., R. Gong, A. Rifai, E.M. Tolbert and L.D. Dworkin, 2007. Long-term, high-dosage candesartan suppresses inflammation and injury in chronic kidney disease: Nonhemodynamic renal protection. J. Am. Soc. Nephrol., 18: 750-759.
8. Wamsley-Davis, A., R. Padda, L.D. Truong, C.C. Tsao, P. Zhang and D. Sheikh-Hamad, 2004. AT_{1A}-mediated activation of kidney JNK1 and SMAD2 in obstructive uropathy: Preservation of kidney tissue mass using candesartan. Am. J. Physiol.-Renal Physiol., 287: F474-F480.
9. Shen, P.C., L.Q. He, X.J. Yang and H.X. Cao, 2012. Renal protection of losartan 50 mg in normotensive Chinese patients with nondiabetic chronic kidney disease. J. Invest. Med., 60: 1041-1047.
10. Rastghalam, R., M. Nematbakhsh, M. Bahadorani, F. Eshraghi-Jazi and A. Talebi *et al*., 2014. Angiotensin type-1 receptor blockade may not protect kidney against cisplatin-induced nephrotoxicity in rats. ISRN Nephrol., Vol. 2014. 10.1155/2014/479645.

11. Maitland, K., L. Bridges, W.P. Davis, J. Loscalzo and M.A. Pointer, 2006. Different effects of angiotensin receptor blockade on end-organ damage in salt-dependent and salt-independent hypertension. Circulation, 114: 905-911.
12. Czechowska, G., K. Celinski, A. Korolczuk, G. Wojcicka and J. Dudka *et al*., 2016. The effect of the angiotensin II receptor, type 1 receptor antagonists, losartan and telmisartan, on thioacetamide-induced liver fibrosis in rats. J. Physiol. Pharmacol., 67: 575-586.
13. Johansen, T.L. and A. Kjaer, 2001. Reversible renal impairment induced by treatment with the angiotensin II receptor antagonist candesartan in a patient with bilateral renal artery stenosis. BMC Nephrol., Vol. 2. 10.1186/1471-2369-2-1
14. Ripley, E. and A. Hirsch, 2010. Fifteen years of losartan: What have we learned about losartan that can benefit chronic kidney disease patients? Int. J. Nephrol. Renovasc. Dis., 3: 93-98.
15. Tuncdemir, M. and M. Ozturk, 2011. The effects of angiotensin-II receptor blockers on podocyte damage and glomerular apoptosis in a rat model of experimental streptozotocin-induced diabetic nephropathy. Acta Histochem., 113: 826-832.
16. Lewis, E.J., 2002. The role of angiotensin II receptor blockers in preventing the progression of renal disease in patients with type 2 diabetes. Am. J. Hypertens., 15: 123S-128S.
17. Noda, M., T. Matsuo, R. Fukuda, M. Ohta and H. Nagano *et al*., 1999. Effect of candesartan cilexetil (TCV-116) in rats with chronic renal failure. Kidney Int., 56: 898-909.
18. Deegan, P.M., C. Nolan, M.P. Ryan, M.A. Basinger, M.M. Jones and K.R. Hande, 1995. The role of the renin-angiotensin system in cisplatin nephrotoxicity. Renal Failure, 17: 665-674.
19. Azzadin, A., J. Malyszko, J.S. Malyszko, A. Tankiewicz, M. Mysliwiec and W. Buczko, 2002. Effects of combination of cyclosporine with losartan or enalapril on kidney function in uremic rats. Pol. J. Pharmacol., 54: 469-473.
20. Callera, G., T. Antunes, J. Correa, D. Moorman and A. Gutsol *et al*., 2016. Differential renal effects of candesartan at high-and ultra-high doses in diabetic mice: Potential role of ACE2/AT2R/Mas. Biosci. Rep., Vol. 36. 10.1042/BSR20160344.
21. Rayner, B.L., Y.A. Trinder, D. Baines, S. Isaacs and L.H. Opie, 2006. Effect of losartan versus candesartan on uric acid, renal function and fibrinogen in patients with hypertension and hyperuricemia associated with diuretics. Am. J. Hypertens., 19: 208-213.