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AMBROXOL AND DESLORATIDINE IN BULK AND PHARMACEUTICAL DOSAGE FORM

Ngatidjan

Department of Pharmacy, Diploma of Pharmacy, Universitas Nahdlatul Wathan Mataram, West Nusa Tenggara, Indonesia

ABSTRACT : Excessive salt consumption is one of the hypertension and kidney disease factors, while telmisartan is one of antihypertensive drugs used in the therapy. Telmisartan not only blocks angiotensin receptor which leads to the decrease of blood pressure, but also activates peroxisome proliferator activated receptor gamma (PPAR-γ) and inhibits transforming growth expression factor of beta-1 (TGFβ-1). Whether telmisartan decreases the kidney collagen volume fraction of excessive NaCl–induced Wistar rats are studied in this experiment.

KEYWORDS: NaCl, telmisartan, TGF-β, collagen.

1. INTRODUCTION

Noncommunicable (NCD) diseases are the world's biggest killer which caused 36 million deaths every year-63% of all deaths globally. Of the 36 million NCD deaths, about 9.1 million were untimely (before 60 years). Three major NCDs (cancers, cardiovascular and diabetes) and threebehavioral risk factors (inappropriate diet, inadequate physical activity, tobacco use and harmful use of alcohol)[1].

The increase of NCD prevalence such as hypertension, diabetes mellitus (DM) and obesity causes the raise of chronic kidney disease (CKD) prevalence about 8% per year. CKD is recently the main and global health problem that the mechanism of preventing and inhibiting the progression of the end stage renal disease (ESRD) is still researched. The primer cause of ESRD is DM 50%, arterial hypertension 27%, glomerulonefritis 13% and other cause 10 percents[2].

Primer or essential hypertension is the main society health problem. In 2005, approximately 1 billion people (14%) globally had hypertension. Hypertension is the main risk factor for cardiovascular, cerebrovascular and kidney diseases that related to the fibrosis occurrence in several organs, such as heart, kidney, liver and cardiovascular[3-4].

The increase of blood pressures usually is caused by combination of many factors. Epidemiologic proofs show that genetic, stress and environmental factor play a role for developmental hypertension[5], but excessive sodium chloride (NaCl) consumption is the main factor which induces hypertension and mainly causes cardiovascular and kidney disease globally[6].The mechanism of blood pressure increases that induced by excessive NaCl is still incomprehensive, but may be related to kidney disability to excrete NaCl in high concentration[7]. The connection between excessive NaCl and blood pressure is still incomprehensive as well and in fact, it is denied by particular social community. Currently many researches focus on the mechanism of kidney destruction by NaCl, sympathetic nerve activity (SNA) increased by baroreflex mechanism and collagen deposition[3].

According to the previous research on animal model, it showed that 8% sodium chloride induced hypertension on *spontaneously hypertensive rats* (SHRs) and *normotensive Wistar-Kyoto rats* (NWKYs)[8]. The induction mechanism is suspected through the activation of angiotensin II by sodium in the way of *aldosterone→endogenous oabain* (EO)[9]. Angiotensin II stimulates vasoconstriction and induces adrenal gland to secrete aldosterone. Furthermore, aldosterone stimulates distal tubulus to reabsorb sodium and water[10-11]. Moreover, angiotensin II induces the change of fibroblast to miofibroblast by pathway of *transforming growth factor-beta1* (TGF-β1). Miofibroblast produces exaggerated extracelluer matrix (ECM), therefore, ECM accumulates in tubulointerstitial area[12].

One of many antihypertensive drugs which widely used is angiotensin receptor blockers (ARBs) such as telmisartan. Telmisartan not only blocks angiotensin receptor, but also plays a role as agonist partial peroxisome proliferator activated receptor-γ (PPAR-γ), so that it activates PPAR-γ[13-14].The activation causes PPAR-γ forms

heterodimer with *retinoid X receptors* (RXRs) so that corepressor is formed that can inhibit gene expression of TGF-β1[15].

According to description above, telmisartantreatment to animal model that be induced with NaCl 8% is potentially suspected to be antifibrotic by measuring collagen volume fraction. Some researchers did a research dealt with the collagen fraction.

2. MATERIALS AND METHOD

Twenty five male Wistars 2.5-3 months of age and 100 – 150 g BW rats were used in this experiment. They were maintained in individual pen and given feed pellet and drinking water adequately. Placed in room temperature 20-24^{0}C, dark-bright cycle for 12 hours. Before doing treatment, animal model was acclimatized for maximal seven days. They were grouped into 5, each consists of rats. Group I (G I) as first negative control did not receive NaCl and telmisartan. G II as second negative control received NaCl but not telmisartan. G III, IV and V received NaCl and telmisartan 3, 6 and 12 mg/ kg BW. The treatments were given every day for 8 weeks. At the day of 56 all rats were sacrificed by dislocating their necks and operating to take the kidney[17-20].40 telmisartan was crushed mortally and then add water until 40 mL. Its suspension was taken by syringe suitable to rats dosage that have been determined to be entered directly to the rats' stomach[16].

Collagen was stained by picrosirius red staining. BMP-7 protein expression and collagen fraction volume was determined by measuring the area of stained tissue within a given field. The area stained was calculated by imageJ software as percentage of the total area within a field[8, 21, 22].

STATICTICAL ANALYSIS

The data are expressed as mean ± standard deviation. They are analyzed by nonparametric test (Kruskal-Wallis). A value of $p<0.05$ was considered statistically significant.

Results

Telmisartan Effect to Collagen Volume Fraction in Kidney of 8% Sodium Chloride-Induced Wistar rats

Intraglomerular and extraglomerular collagen volume fraction were lower in kidney of telmisartan-treated Wistar rats than negative control group. Based on Table 5, Table 6 and Figure 2 that intraglomerular and extraglomerular collagen volume fraction of group V < group II.

Table 5.Intraglomerular collagen volume fraction (group I and II=negative control, group III, IV and V=8%NaCl +telmisartan3, 6 and12 mg/kg BW)

Group	collagen volume fraction (%) of rat number:					Mean±SD	p
	1	2	3	4	5		
I	28,5	10,6	32,6	36,4	14,15	24,45±11,4	0,01*
II	28,9	55,6	45,9	36,8	26,20	38,68±12,1**	
III	47,5	41,0	43,1	15,8	32,90	36,06±12,5	
IV	41,4	45,0	36,5	36,6	24,30	36,76±7,8	
V	8,10	14,4	31,1	6,10	14,20	14,78± 9,8**	

*significant difference of mean inWistar rat group ($p<0.05$)
**significant difference of mean inWistar rat group II and group V ($p<0.05$)

Table 6.Extraglomerular collagen volume fraction (group I and II=negative control, group III, IV and V=8% NaCl +telmisartan 3, 6and12 mg/kg BW)

Group	Collagen volume fraction (%) rat number:					Mean±SD	p
	1	2	3	4	5		
I	17,6	2,83	15,1	15,1	8	11,72±6,1	0,059
II	17,7	49,8	23,2	38,9	10,4	28,00±16,0	
III	15,5	23,9	21,3	9,40	19,6	17,94±5,6	
IV	23,7	16,5	26,4	28,4	19,2	22,84±4,9	

V	15,5	10,9	22,6	5,25	17,0	14,25±6,5

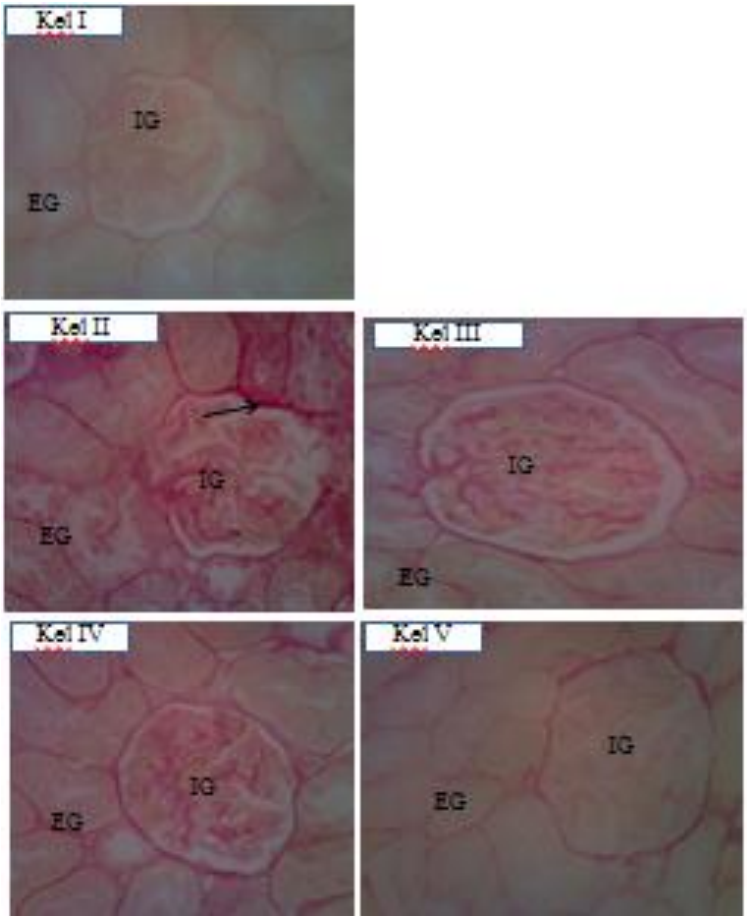

Figure 2.Microscopic picture of kidney slide in 400× magnification for group I, II, III, IV and V that have been stained by picrosirius red staining (pink color → shows cells express collagen). IG=intraglomerular, EG=extraglomerular.

3. DISCUSSION

Cox *et al.* expressed salt can induce fibrosis on heart, kidney and cardiovascular that be proved from two separated cohort studiesin human population[4]. Yu *et al.* also revealed salt induces fibrosis in kidney, left ventricle and intramioacrdial artery of SHRs and WKYs. Kidney fibrosis causesend stage renal disease (ESRD) which worsen the kidney condition[8]. Fibrosis induction in kidney increases blood pressure and induces chronic and acute kidney disease.

The increase of TGF-β1 bioactivity caused the raise of kidney collagen synthesis. According to the previous research on artery Wistar rats showed that 8% NaCl increases collagen fraction volume, blood pressure, media thickness, lumen diameter, media and lumen ratio and percentage of PCNA positive expression than control group ($p<0.05$), meanwhile telmisartan decreased those variable than item of control group ($p<0.05$). Thus, salted food can increase blood pressure and reduce ion pomp activity; meanwhile telmisartan inhibits vascular smooth muscle proliferation, collagen accumulation and hypertension prevention[23].

Finally, telmisartan reduces the expression of TGF-β1 as a result, the decrease of collagen volume fraction.

4. CONCLUSION AND SUGGESTION

In conclusion, intraglomerular and extraglomerular collagen volume fraction were lower in 8% sodium chloride-induced and telmisartan-treated male Wistar rats compared with negative control group items.

REFERENCES

1. World Health Organisation (WHO), 2010. *Global Status Report on Noncommunicable Diseases*. Geneva, Switzerland.
2. Baltatzi, M., Ch, S. and Hatzitolios, A., 2011. Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension of chronic kidney disease and renoprotection. *Hippokratia* 15(1):27–32.
3. Blaustein, M.P., Leenen, F.H.H., Chen L., Golovina, V.A., Hamlyn, J.M., Pallone, T.L., Huysse, J.W.V., Zhang, J. and Wier, W.G., 2012. How NaCl raises blood pressure: a new paradigm for the pathogenesis of salt-dependent hypertension. *Am. J. Physiol. Heart. Circ. Physiol.* 302:H1031–H1049, 2012
4. Cox, N., Pilling, D. and Gomer, R.H., 2012. NaCl Potentiates Human Fibrocyte Differentiation. *Plos One* 7(9):1-9.
5. Beevers, G., Lip, G.Y.H. and O'Brien, E., 2001. ABC of Hypertension "The Pathophysiology of Hypertension". *BMJ* 322: 912-916.
6. He, F.J., Jenner, K.H., MacGregor, G.A. and Avenue, G., 2012. Telmisartan exerts renoprotective actions via peroxisome. *Hypertension.* 59:308-316.
7. Meneton, P., Jeunemaitre, X., Wardener, H. E. D. E. and Macgregor, G. A., 2005. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol. Rev*. 86:679–715.
8. Yu, H. C. M., Burrell, L. M., Black, M. J., Wu, L. L., Dilley, R. J., Mark, E. and Johnston, C. I., 1998. Salt induces myocardial and renal fibrosis in normotensive and hypertensive rats. *Circulation* 98:2621–2628.
9. Leenen, F. H. H., 2010. The central role of the brain aldosterone –"ouabain" pathway in salt-sensitive hypertension. *BBA-Mol. Basis Dis.* 1802:1132–1139.
10. Dendorfer, A. and Dominiak, P., 2004. Cardiovascular and renal function of angiotensin II type-2 receptors. *Cardiovasc. Res.* 62:460–467.
11. Starr, C. and McMillan, B., 2012. *Human Biology. 9th Edition*. Brooks/Cole Cengage Learning, Canada.
12. Mezzano, S.A., Ruiz-Ortega, M. and Egido, J., 2001. Angiotensin II and renal fibrosis. *Hypertension.* 38:635-638.
13. Chambers, S., 2008. Telmisartan an effective antihypertensive for 24-hour blood pressure control. *Drugs in Context*. 4(1):1–14.
14. Funao, K., Matsuyama, M., Kawahito, Y., Sano, H., Chargui, J., Touraine, J. and Yoshimura, R., 2009. Telmisartan as a peroxisome proliferator-activated receptor-Á ligand is a new target in the treatment of human renal cell carcinoma. *Mol. Med. Rep.* 2:193-198.
15. Rotman, N. and Wahli, W., 2010. PPAR modulation of kinase-linked receptor signaling in physiology and disease. *Physiology* 25:176–185.
16. Xu, L. and Liu, Y., 2013. Administration of Telmisartan Reduced Systolic Blood Pressure and Oxidative Stress Probably Through the Activation of PI3K/Akt/eNOS Pathway and NO Release in Spontaneously Hypertensive Rats. *Physiol. Res.* 62: 351-359.
17. Younis, F., Stern, N., Limor, R., Oron, Y., Zangen, S. and Rosenthal, T., 2010. Telmisartan ameliorates hyperglycemia and metabolic profile in nonobese Cohen-Rosenthal diabetic hypertensive rats via peroxisome proliferator activator receptor–γ activation. *Metab.-Clin.Exp.* 59(8):1200-1209.
18. Matsumura, T., Kinoshita, H., Ishii, N., Fukuda, K.,Motoshima, H., Senokuchi, T.,Taketa, K., Kawasaki, S.,Nishimaki-Mogami, T., Kawada, T., Nishikawa, T. and Araki, E., 2011. Telmisartan exerts antiatherosclerotic effects by activating in macrophages. *Arterioscler. Thromb. Vasc. Biol.* 31:1268-1275.
19. Liu, W., Wang, W., Song. S.W., Gu, X.F., Ma, X.J., Su, F.Y., Zhang, H., Liu, A.J. and Su, D.F., 2011. Synergism of telmisartan and amlodipine on blood pressure reduction and cardiorenal protection in hypertensive rats. *J. Cardiovasc. Pharmacol.* 57(3):308-16.
20. Jawi, I. M., Yasa, I. W. P. S., Suprapta, D. N. and Mahendra, A. N., 2012. Antihypertensive effect and eNOS expressions in NaCl-induced hypertensive rats treated with purple sweet potato. *Univ. J. Med. Dent* 1(9): 102-107.
21. Lync, M. J., Raphael, S.S., Mellor, L.D., Spare, P.D. and Inwood, M.J.H., 1969. *Medical Laboratory Technology and Clinical Pathology*. W.B. Saunders Company, United States of America (USA).
22. Fatchiyah, Arumingtyas, E.L., Widyarti, S., and Rahayu, S., 2011. *Biologi Molekuler "Prinsip Dasar Analisis"*. Erlangga, Jakarta.
23. Shang, Q.H., Min, X.Q., Liu, C., Mao, W.H., Shang, Q.H., 2012. Effects Of High Salt Diet On Arterial Remodelling And The Intervention Of Telmisartan In Wistar Rats. *Heart.* 98 (2): E1– E319.