Severe acute interstitial nephritis induced by valsartan
A case report

Tong Chen, PhD, Peng-cheng Xu, PhD, Shui-ya Hu, PhD, Tie-kun Yan, MSc, Jian-Qing Jiang, MD, Jun-ya Jia, PhD, Li Wei, MSc, Wen-ya Shang, MSc

Abstract
Rationale: Angiotensin receptor blocker (ARB) can increase serum creatinine or potassium levels in patients with renal insufficiency, renal artery stenosis, heart failure or hypovolemia, but hardly cause severe kidney injury in patients without any risk factors. A case of severe acute interstitial nephritis (AIN) induced by valsartan was reported here.

Patient concerns: A 62-year-old female with nausea for 1 month and acute deterioration of kidney function for 2 weeks was admitted. She had a history of hypertension for 5 months and had taken valsartan 40mg daily for 4 months. Although the valsartan had been stopped for 2 weeks, the serum creatinine continuously increased after admission. Kidney biopsy demonstrated the eosinophils infiltration in interstitium.

Diagnoses: AIN induced by valsartan.

Interventions: The patient was treated with glucocorticoid.

Outcomes: The serum creatinine decreased gradually and got back to normal level 5 months later. Then therapy of glucocorticoid was stopped. Renal artery stenosis was excluded by computed tomography angiography (CTA).

Lessons: Although valsartan-induced allergy has been reported previously, AIN was firstly recognized as a severe complication of this drug. We suggest when there is a ARB-associated continuous deterioration of kidney function for patients without renal insufficiency, renal artery stenosis, heart failure or hypovolemia, AIN should be thought of and therapy with glucocorticoid should be considered if necessary.

Abbreviations: AIN = acute interstitial nephritis, ARB = angiotensin receptor blocker, CTA = computed tomography angiography.

Keywords: acute interstitial nephritis, case report, kidney biopsy, valsartan

1. Introduction
Angiotensin receptor blocker (ARB) is one of renin angiotensin system (RAS) blockers and is commonly used as an antihypertensive drug. It can also reduce urinary protein and protect heart function. The ARB has some potential side effects of increasing serum creatinine and potassium levels due to its effect of reducing renal hemoperfusion.\[1,4\] According to the previous studies, these side effects mainly occur in patients with pre-existing kidney dysfunction, renal artery stenosis, heart failure or hypovolemia. Therefore, ARB are generally safe for patients who do not have these risk factors.\[3,4\] However, like angiotensin-converting enzyme inhibitors (ACEI) which is an another RAS blocker,\[15\] ARB also cause allergic reactions in some patients.\[6,7\] Although ACEI such as captopril has been demonstrated to induce acute interstitial nephritis (AIN),\[7,8\] ARB-induced AIN has not been reported before. We reported a case of severe acute kidney injury after valsartan treatment. All risk factors were excluded by careful examination. Percutaneous kidney biopsy confirmed the renal failure was caused by AIN. Renal function returned to normal after treatment with corticosteroid. This case reminds us that we should closely monitor the renal function for all patients receiving ARB therapy.

1.1. Ethics approval and consent to participate
The Ethics Committee of Tianjin Medical University General Hospital gave approval for the publication of this case report (IRB2018-002-01), and patient has provided informed consent for publication of the case.
1.2. Case report

A 62-year-old female with nausea for 1 month and increased serum creatinine for 2 weeks was admitted. She did not have a history of chronic kidney disease and the serum creatinine was 1.01 mg/dL when she did routine physical examination 13 months ago. She had a history of hypertension for 5 months and had taken valsartan dispersible tablets (Lunan pharmaceutical group, Shandong, China) 40 mg daily for 4 months. Two weeks before admission, she stopped the valsartan since serum creatinine showed as high as 4.29 mg/dL. Pertinent physical examination findings were normal except a hypertension of 160/100 mm Hg. Abdominal ultrasonography showed no obvious abnormality of 2 kidneys. Echocardiogram showed slight left ventricular hypertrophy with a normal ejection fraction 61%. Blood routine showed a mild anemia with hemoglobin 101 g/L, Total white blood cells counts and eosinophils counts were normal. Serum creatinine increased to 5.60 mg/dL. Urinalysis revealed glucosuria 2+ (Fasting blood glucose was 5.8 mmol/L), leukocytoria 1+ and proteinuria 1+. The 24h urine protein excretion revealed 0.2596 grams (normal range was below 0.15 grams). Urine N-acetyl-beta-D-glucosamidase was increased (21.2 U/g creatinine, normal range was 1.1–12.0 U/g creatinine).

Immunologic examinations were normal except a slight rise of C-reactive protein (0.89 mg/dL, normal range was below 0.8 mg/dL).

Serum creatinine was reviewed 2 days later and the result showed as high as 5.75 mg/dL. Then kidney biopsy was performed immediately. Light microscopy showed no obvious abnormality of glomeruli (Fig. 1A), while there were obvious inflammatory changes in the interstitium with increased eosinophils infiltration. There were also mild interstitial fibrosis and tubular injury (Fig. 1B). Immunofluorescence showed no immune complex deposition. The AIN was diagnosed and the patient was given intravenous methylprednisolone 40 mg daily. One week later the serum creatinine decreased to be 5.67 mg/dL, then the patient was discharged with oral methylprednisolone 20 mg daily. Levamisolpine besylate 5 mg daily was given in order to control hypertension.

During follow-up for 5 months, the serum creatinine decreased gradually and the glucocorticoid was tapered (Fig. 2). Her serum creatinine had recovered to normal before the follow-up on August 4th 2018. To exclude renal artery stenosis, computed tomography angiography (CTA) was done. The results showed no abnormality for bilateral renal arteries (Fig. 3).

2. Discussion

Until now, the pathogenic mechanism of anaphylaxis caused by ARB has remained unclear. Losartan, which is the 1st marketed ARB, has been reported to cause lymphoid hyperplasia, vasculitis, and angioneurotic edema in literature. Valsartan-associated allergy is similar to losartan including drug eruption, angioedema and mucocutaneous bullous pemphigoid (Table 1). Drug eruption of valsartan is relatively common in clinic and usually start after weeks to 1 month of therapy. To our knowledge, this is the 1st case of AIN caused by valsartan (The Naranjo score is 5). The AIN mainly injure the tubules and interstitium and causes acute to subacute deterioration of kidney function. The pathophysiology of AIN is induced by a hypersensitive allergic reaction to an offending agent with the activation of eosinophils causing inflammatory infiltrates in the interstitium of kidney. Most AIN is due to non-steroidal anti-inflammatory drugs and antibiotics. A kidney biopsy is required to confirm the diagnosis of AIN. Supportive findings including eosinophils in urine or blood in laboratory testing can help to diagnose. None of the preceding clinical findings is sensitive or specific to AIN. In the present study, when the patient was admitted, the possibility of AIN was considered because the serum creatinine increased rapidly and valsartan was the only drug used before admission. However, the diagnosis of AIN could not be confirmed for our patient until the kidney biopsy demonstrated the infiltration of eosinophils in the interstitium.

Since ARB could cause severe increase of serum creatinine in patients with pre-existing kidney dysfunction, renal artery stenosis, heart failure or hypovolemia, all these risk factors were carefully checked for our patient. After reviewing the history and doing echocardiogram examination, the pre-existing kidney dysfunction, heart failure and hypovolemia were easily excluded. However, the exclusion of the renal artery stenosis was difficult because the patient had a new-onset hypertension and the high level of serum creatinine did not allow doing imaging examination which needed contrast. Fortunately, the patient got complete recovery of kidney function 5 months later and a CTA excluded the renal artery stenosis at last.
The AIN is a dose-independent allergic reaction. The time from exposure to appearance of symptoms is widely variable and can be from a few days to years.\(^{[22,23]}\) In the current study, the patient only took valsartan 40mg daily. We thought the low dose of drug postponed the occurrence of AIN. The patient felt nausea after 2 months of valsartan therapy, but she did not test kidney function at that time. Generally speaking, mild increase of serum creatinine does not cause nausea. So we speculated the

**Figure 2.** The clinical course of the patient. Since the kidney function recovered, CTA was done to excluded renal artery stenosis. The glucocorticoid was stopped before the examination of CTA. CTA = computed tomography angiography.

**Figure 3.** The CTA examination for renal artery. Iohexol was used as contrast. No stenosis was found for bilateral renal arteries. CTA = computed tomography angiography.
appearance of AIN should be earlier than the appearance of nausea.

Controversy exists about whether corticosteroid therapy is necessary in the treatment of drug-induced AIN. Some studies have reported corticosteroid induced a more rapid and complete recovery of kidney function, while the others have failed to confirm the results.[24-27] In a recent research, Quinto LR et al made a systemic review of 8 retrospective studies comparing the effects of corticosteroid therapy versus non-corticosteroid therapy in the treatment of drug induced AIN.[28] Four studies showed no difference in serum creatinine between corticosteroid and non-corticosteroid therapy, while 4 studies found a benefit of corticosteroid therapy. Regrettfully, a meta-analysis was not performed due to considerable heterogeneity. The authors proposed larger well-designed trials are needed to draw a conclusion. In the present study, the deterioration of kidney function did not cease although valsartan had been discontinued for 2 weeks. In order to accelerate the recovery of kidney function, glucocorticoid was administrated after kidney biopsy. Although the serum creatinine decreased slowly, the patient got complete kidney recovery after treatment for 5 months.

3. Conclusion

This is the 1st case of valsartan-induced AIN. We suggest when the serum creatinine decreased slowly, the patient got complete kidney recovery after treatment for 5 months. The deterioration of kidney function did not cease although valsartan had been discontinued for 2 weeks. In order to accelerate the recovery of kidney function, glucocorticoid was administrated after kidney biopsy. Although the serum creatinine decreased slowly, the patient got complete kidney recovery after treatment for 5 months.

Author contributions

Conceptualization: Peng-cheng Xu.
Data curation: Jian-Qing Jiang.
Project administration: Li Wei, Wen-ya Shang.
Supervision: Tie-kun Yan.
Visualization: Shui-yi Hu.
Writing – original draft: Tong Chen.
Writing – review & editing: Jun-ya Jia.

References

[1] Gao F, Yao M, Cao Y, et al. Valsartan ameliorates podocyte loss in diabetic mice through the Notch pathway. Int J Mol Med 2016;37:1328–36.
[2] Schmidt M, Mansfeld KE, Bhaskaran K, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. BMJ 2017;356:j791.
[3] Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) Project. J Am Heart Assoc 2017;6:e005428.
[4] Mathiesen L, Severn A, Guthrie B. Monitoring and adverse events in relation to ACE inhibitor/angiotensin receptor blocker initiation in people with diabetes in general practice: a population database study. Scott Med J 2015;38:69–76.
[5] Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: a review of the literature. J Clin Hypertens (Greenwich) 2017;19:1377–82.
[6] Thalayayar MP, Fajt ML, Birnie KM, et al. Angiotensin receptor blocker-induced visceral angioedema. J Investig Allergol Clin Immunol 2015;25:63–4.
[7] Smith WR, Neill J, Cushman WC, et al. Captopril-associated acute interstitial nephritis. Am J Nephrol 1989;9:230–5.
[8] Viraben R, Lamant L, Brousset P. Losartan-associated atypical cutaneous lymphoid hyperplasia. Lancet 1997;350:1366.
[9] Piérard-Framonct C1, Henry F, Piérard GE. Severe purpural and polymorphous vasculitis caused by losartan. Ann Dermatol Venereol 2001;128:1040–2.
[10] Kazim SF, Shahid M, Losartan associated anaphylaxis and angioneurotic oedema. J Pak Med Assoc 2010;60:685–6.
[11] Mustasim DF. Lymphomatoid drug eruption mimicking digitate dermatossscross reactivity between two drugs that suppress angiotensin II function. Am J Dermatopathol 2003;25:331–4.
[12] Geylon G, Ceylan C, Kazandi AG. Linear lichenoid drug eruption induced by valsartan. Clin Exp Dermatol 2009;34:e334–5.
[13] Sawada Y, Yoshiki R, Kawakami C, et al. Valsartan-induced drug eruption followed by CD30+ pseudolymphomatous eruption. Acta Derm Venereol 2010;90:521–2.
[14] Ozturk G, Turk BG, Senturk B, et al. Exanthematous drug eruption due to valsartan. Cutan Ocul Toxicol 2012;31:335–7.
[15] Frey CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. Pharmacotherapy 1998;18:866–8.
[16] de la Serna Figuera C. Angioedema and urticarial reaction induced by valsartan. Med Clin 2000;114:599.
[17] Martínez Alonso JC, Domínguez Ortega FJ, Méndez Alcalde J, et al. Angioedema due to valsartan. Allergy 2003;58:367.
[18] Iorns BK, Kumar A. Valsartan-induced angioedema. Ann Pharmacother 2003;37:1024–7.
[19] Shino M, Takahashi K, Murata T, et al. Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis. Am J Otolaryngol 2011;32:624–6.
[20] Cala A, Cooley C, Palaniwamy C, et al. Valsartan-induced angioedema in a patient on angiotensin-converting enzyme inhibitor for years: case report and literature review. Am J Ther 2012;19: e189–92.
[21] Femiano F. Mucocutaneous bullous pemphigoid induced by valsartan. A clinical case. Minerva Stomatol 2003;52:187–90.
[22] Chamard G, Kamboj M, Olaoye OA, et al. Acute interstitial nephritis: a multifaceted disease. Clin Case Rep 2018;6:946–7.
[23] Raghavan R, Shaver S. Mechanisms of drug-induced interstitial nephritis. Adv Chronic Kidney Dis 2017;24:64–71.
[24] Fernandez-Juarez G, Perez JV, Caravaca-Fontán F, et al. Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. Clin J Am Soc Nephrol 2018;13: 1851–8.

[25] Chowdry AM, Azad H, Mir I, et al. Drug-induced acute interstitial nephritis: prospective randomized trial comparing oral steroids and high-dose intravenous pulse steroid therapy in guiding the treatment of this condition. Saudi J Kidney Dis Transpl 2018;29: 598–607.

[26] Nast CC. Medication-induced interstitial nephritis in the 21st Century. Adv Chronic Kidney Dis 2017;24:72–9.

[27] Moledina DG, Perazella MA. Treatment of drug-induced acute tubulointerstitial nephritis: the search for better evidence. Clin J Am Soc Nephrol 2018;13:1783–7.

[28] Quinto LR, Sukkar L, Gallagher M. The effectiveness of corticosteroid compared to non-corticosteroid therapy for the treatment of drug-induced acute interstitial nephritis: a systematic review. Intern Med J [Epub ahead of print].