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【 CASE REPORT 】

Quetiapine-related Acute Kidney Injury Requiring Transient Continuous Hemodiafiltration

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Abstract:
A 73-year-old man, with congestive heart failure due to combined valvar disease, underwent curative surgery. Although the surgery was successful, his clinical course was eventful because of pulmonary complications, and he began to deteriorate mentally. Quetiapine was prescribed, which appeared to effectively settle his mental status. Following the administration of quetiapine, however, he developed acute kidney injury (AKI) that required continuous hemodiafiltration. Subsequent to discontinuation of quetiapine, his renal function gradually improved. Atypical antipsychotic drugs, including quetiapine, are frequently used to treat delirium in elderly patients in the intensive-care setting. This case highlights a potential risk of quetiapine-related AKI.

Key words: acute kidney injury, acute tubular necrosis, atypical antipsychotic drug, continuous hemodiafiltration, quetiapine

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Introduction

Quetiapine is frequently prescribed for treating delirium in elderly patients in the intensive-care setting. Recently, the potential risk of acute kidney injury (AKI) with the use of atypical antipsychotic drugs was reported in a large observational study (1). However, few reports have described a close case study. Accordingly, the detailed etiology of AKI has yet to be explained.

We herein report a case of quetiapine-related AKI in an elderly post-operative man requiring continuous hemodiafiltration (CHDF) prior to the discontinuation of quetiapine administration.

Case Report

A 73-year-old man with severe aortic regurgitation due to infective endocarditis, complicated with severe mitral and tricuspid regurgitation, was transferred to our hospital for the treatment of congestive heart failure. He was also complicated with chronic atrial fibrillation, pulmonary arterial aneurysm, hepatic dysfunction due to chronic congestive liver, and pancytopenia of unknown cause. On admission, he had clinical symptoms of heart failure and was graded as New York Heart Association Class IV. His blood pressure was 170/40 mmHg with an irregular pulse rate of 72 beats/min.

The liver was palpable approximately 4 cm below the right costal margin. A prominent systolic murmur at the cardiac apex and a diastolic murmur at the fourth left sternal border were audible and classified as Levine grade III/VI. A third heart sound was also audible. Bilateral coarse crackles in his lower lung field were noted on chest auscultation. Slight pitting edema was observed in the distal lower limbs. Chest radiography showed cardiomegaly (cardiothoracic ra-

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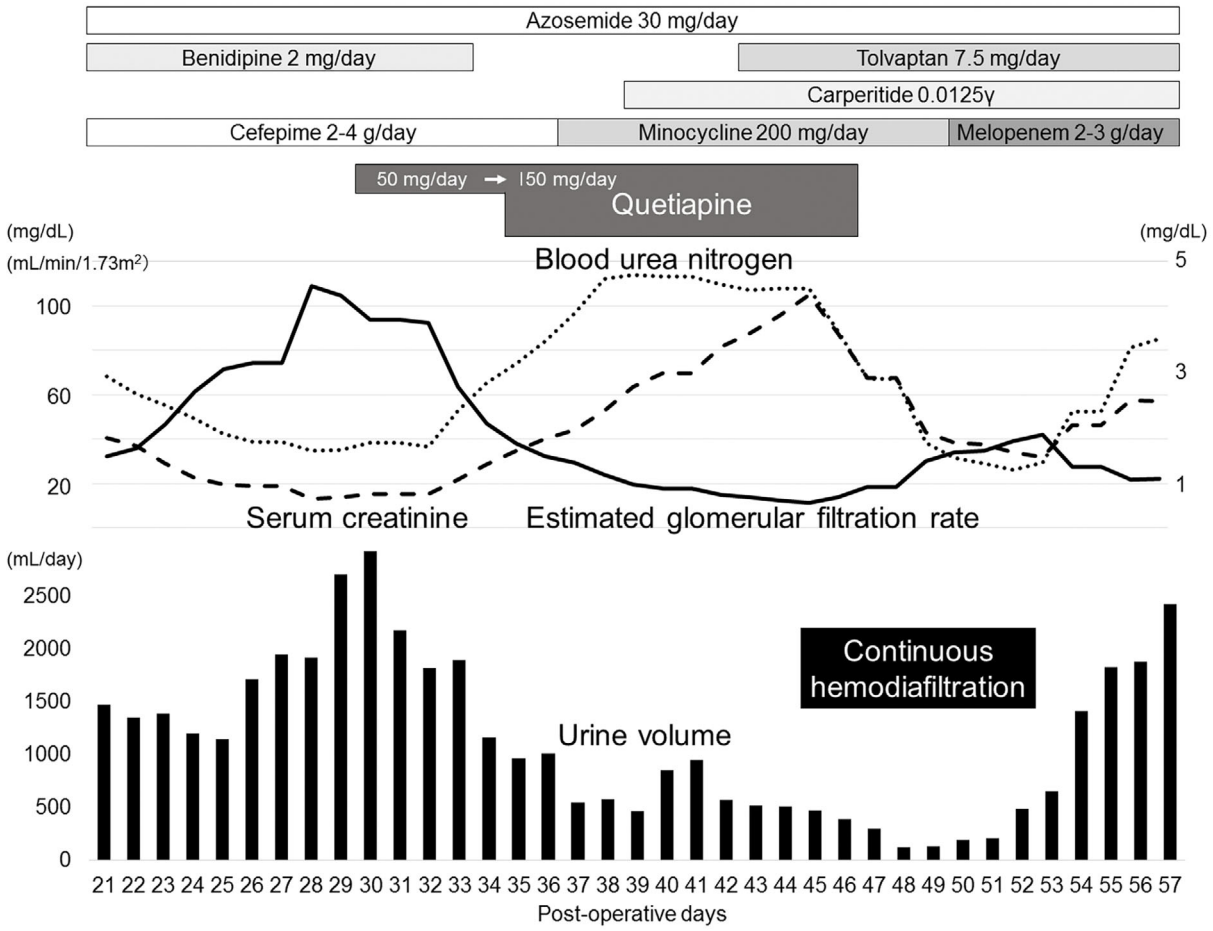

Figure. **Clinical course of quetiapine-related acute kidney injury. After the administration of quetiapine, the renal function began to be exacerbated. The renal function did not improve even after suspending benidipine and cefepime or with the additional administration of carperitide followed by tolvaptan. Continuous hemodiafiltration was initiated 15 days after the prescription of quetiapine. Quetiapine was discontinued 17 days after the first administration. Approximately one week after this discontinuation, the patient's renal function started to improve gradually, along with the recovery of the urine volume. Continuous hemodiafiltration was terminated six days after stopping quetiapine.**

tio, 56.5%) with a prominent pulmonary trunk silhouette and bilateral pleural effusion with congestion.

An intravenous continuous drip infusion, including dobutamine, carperitide, and furosemide, was initiated soon after admission. However, the decompensated heart failure had been difficult to control because of complicated unexpected sequelae, including diffuse alveolar hemorrhaging and repeated aspiration pneumonia, which occurred during the course of medical management. After repeated attempts at tracheal intubation, he finally underwent aortic valve replacement, mitral and tricuspid annuloplasty, left atrial appendage closure, and pulmonary artery reconstruction 60 days after admission. No anticoagulants had been administered during the peri-operative period because of his baseline pancytopenia and history of diffuse alveolar hemorrhaging before the surgery.

Two days after the successful surgery, he was discharged from the intensive-care unit. Unfortunately, however, immediately after his transfer to the general ward, he developed massive aspiration pneumonia, which again required mechanical ventilation. Although melopenem therapy was temporarily effective for the pneumonia, his ensuing clinical course was further complicated with subsequent right empyema. *Enterococcus cloacae* was detected after thoracentesis of the empyema fluid. Thus, cefepime administration was started on post-operative day (POD) 18. However, antibiotics were clinically ineffective to eradicate the multiple encapsulated empyema. He suffered from a fever of around 38-39℃ with elevated C-reactive protein around 15 mg/dL. Several attempts at pleural drainage and lavage were also ineffective. Because of repeated aspiration pneumonia and drug-refractory empyema, he finally underwent tracheostomy on POD 20. After tracheostomy, the patient's renal function kept improving (Figure), and his body weight remained approximately 45-46 kg. No hemodynamic or echocardiographic findings indicating either dehydration or a low-output state were observed.

Because of the much longer and far more complicated

Table 1. Laboratory Data Just before the Administration of Quetiapine.

Peripheral blood		Uric acid	2.2 mg/dL
White blood cells	6,200 /μL	Total protein	5.9 g/dL
Red blood cells	283×10⁴ /μL	Serum albumin	1.7 g/dL
Hemoglobin	8.6 g/dL	Aspartate aminotransferase	60 IU/L
Hematocrit	26.9 %	Alanine aminotransferase	44 IU/L
Platelets	3.4×10⁴ /μL	Alkaline phosphate	405 IU/L
		γ-glutamyl transpeptidase	166 IU/L
Blood coagulation		Creatine kinase	100 IU/L
Activated partial thromboplastin time	35.3 sec	Lactate dehydrogenase	274 IU/L
Prothrombin time	64.7 %	Choline esterase	81 U/L
Prothrombin time-international normalized ratio	1.26	Brain natriuretic peptide	432 pg/mL
D-dimer	10.7 μg/mL	Total bilirubin	0.8 mg/dL
		Direct bilirubin	0.2 mg/dL
Biochemistry		C-reactive protein	11.87 mg/dL
Sodium	137 mEq/L		
Potassium	4.0 mEq/L	Hepatitis B virus antigen	(-)
Chloride	97 mEq/L	Hepatitis C virus antibody	(-)
Calcium	7.6 mg/dL		
Blood urea nitrogen	35.1 mg/dL	Anti-neutrophil cytoplasmic antibodies (ANCA)	
Serum creatinine	0.57 mg/dL	Perinuclear-ANCA	<0.1 U/mL
Estimated glomerular filtration rate	104.7 mL/min/1.73m²	Cytoplasmic-ANCA	<0.1 U/mL

Table 2. The Urinalysis Findings during Acute Kidney Injury.

Color	Light yellow
pH	5
Specific gravity	1.011
Protein	1+
Occult blood	2+
Sedimentation	
Red blood cells	30-49/HPF
Dysmorphic red blood cells	-
White blood cells	5-9/HPF
Eosinophils	not available
Epithelial cell casts	1+
Granular casts	1+
Waxy casts	1+
N-acetyl-beta-D-glucosaminidase	78.7 U/L
Osmolality	321 mOsm/L
β2 microglobulin	93 μg/L
Sodium	61 mmol/L
Urea nitrogen	289 mg/dL
Fractional excretion of sodium	7%
Fractional excretion of urea nitrogen	41%

HPF: high power field

pre- and post-operative clinical course than the patient had expected, his mental functions began to deteriorate. Delirium, refusal of medical treatments, disregard and violence towards medical staff, and insomnia began to manifest. The patient ultimately required intervention by the Psychiatry Department. Quetiapine at 50 mg/day was prescribed on POD 30, which was then increased to 150 mg/day on POD 35. Table 1 shows the laboratory data on POD 29, just before quetiapine treatment was begun. Although quetiapine seemed to be effective, the patient's renal function began to decline soon after the first dose was administered (Figure). During the exacerbation of his renal function, his hemodynamics were stabilized, and echocardiography helped confirm a normal cardiac function without any significant valvar disease or signs suggestive of heart failure. Combined with the urinalysis and ultrasonography findings, both pre-renal azotemia and post-renal azotemia were ruled out.

Initially, we considered cefepime to be the cause of the drug-induced AKI. However, the renal function did not improve even after discontinuing cefepime on POD 37. On POD 43, the estimated glomerular filtration rate further decreased to 13.7 mL/min/1.73 m², compared with 104.7 mL/min/1.73 m² on POD 29 (Table 1). A urine examination on POD 43 was compatible with acute tubular necrosis (ATN) with elevated N-acetyl-β-D-glucosaminidase and tubular casts (Table 2). The patient's body weight increased from 45.3 kg to 55.5 kg due to a decrease in the urine volume. With the diagnosis of AKI, carperitide (POD 39) followed by tolvaptan (POD 43) was subsequently administered to increase the urine volume (Figure). However, these agents were not effective, which led us to initiate CHDF 15 days after prescription of quetiapine (POD 45). The patient's renal function and urine volume did not improve; we therefore discontinued quetiapine 17 days after the first administration (POD 47). Approximately one week after the discontinuation of quetiapine, his renal function started to improve gradually, and the urine volume increased (Figure). The patient underwent a total of nine days of CHDF, ending six days after quetiapine (POD 53) was suspended. His general condition improved without any recurrence of AKI. After a subsequent rehabilitation period, the patient was discharged on POD 108. Finally, just before the discharge, the esti-

mated glomerular filtration rate recovered to 75.4 mL/min/1.73 m^2.

Discussion

Quetiapine was selected for the present case to relieve the patient's post-operative delirium, which consisted of insomnia, irascibility, and refusal of any treatment due to prolonged post-operative complications. Quetiapine is a dibenzothiazepine derivative classified as an atypical antipsychotic drug (2). Quetiapine has moderate affinity for serotonin ($5HT_2$), adrenergic (α_1), muscarinic, and histaminergic receptors; a minor affinity for serotonin ($5HT_1$) and dopamine (D 2) receptors; and a very low affinity for adrenergic (α_2) and dopamine (D1) receptors. Pharmacokinetic studies in humans have shown that at least 73% of quetiapine is absorbed after its oral administration, with a median time to reach the maximum plasma concentration of 1-2 hours. The liver is the primary route of metabolism, with metabolites mainly excreted in the urine. Approximately 83% of the unmetabolized quetiapine binds to serum proteins. The remaining 17% of free unmetabolized quetiapine is considered to be responsible for the main pharmacological activity (2).

The patient had no baseline renal insufficiency and had been showing stable hemodynamics after a successful surgical procedure. Although quetiapine had surely improved his psychotic symptoms, AKI (3) developed three days after the prescription of quetiapine to such a degree that CHDF was required. Renin-angiotensin-aldosterone system inhibitors had not been administered in this patient, and other drugs, including benidipine and antibiotics, were excluded as the cause of AKI. Approximately one week after stopping quetiapine, the urine volume started to recover, and CHDF was safely withdrawn. The prompt improvement in the renal function data just after starting CHDF (Figure) was the apparent effect of CHDF, and the recovery in the urine volume approximately one week after the discontinuation of quetiapine is more in line with the course of drug-induced ATN. For these reasons, the main cause of the AKI was considered to be quetiapine-related nephrotoxicity. If quetiapine had not been discontinued, then the suspension of CHDF would have been further delayed, and thus it might not have been possible to withdraw CHDF for nine days.

The use of an atypical antipsychotic drug has been associated with an increased 90-day risk for hospitalization with AKI (1). However, the detailed etiology of the AKI has yet to be clarified. Quetiapine-related AKI has been reported in several cases in association with hypotension, ventricular arrhythmias, acute urinary retention, rhabdomyolysis, malignant syndrome, and thrombotic thrombocytopenic purpura (1, 4-6). In the present case, however, no clinical findings indicating these specific etiologies were observed.

The urinalysis data, including a fractional excretion of urea nitrogen of >35%, increased urinary N-acetyl-β-D-glucosaminidase activity, and detection of tubular casts, indicated the involvement of a renal factor rather than a pre-renal factor, or more specifically ATN. As shown in this case (Table 2), when natriuretic diuretics are being administered, the fractional excretion of sodium is unsuitable for differentiating renal factors from pre-renal factors. Drug-induced nephrotoxicity is classified into three categories: that involving glomerulonephritis, that involving acute interstitial nephritis (AIN), and that involving ATN. ATN is the most common form of renal injury resulting from nephrotoxin exposure (7). Glomerular disease was unlikely to be the culprit in the present case, as no significant dysmorphic red blood cells in the urine had been detected. Similarly, no findings indicating AIN, including significant leukocyturia; allergic symptoms, including rash; or eosinophilia (8, 9), were detected. The improvement in the renal function after simply stopping the quetiapine also supported ATN rather than AIN as the underlying mechanism for the AKI observed. Although the definite differential diagnosis of ATN and AIN should be made by performing a renal biopsy (9), a biopsy was not performed in the present case because of the patient's poor general condition with multiple complications, including pancytopenia and empyema.

A history of alveolar hemorrhaging as well as hematuria during AKI suggests the possibility of rapidly progressive glomerulonephritis. Although the anti-glomerular basement membrane antibody level was not determined in the present case, no physical findings compatible with vasculitis were observed. Furthermore, perinuclear- as well as cytoplasmic-anti-neutrophil cytoplasmic antibodies were both negative. The renal functional recovery without any immunosuppressive treatments also supported drug-related AKI.

The administration of antibiotics, as well as several attempts at performing pleural drainage and lavage all proved to be clinically ineffective for eradicating the multiple encapsulated empyema, and an abnormal coagulation profile was observed (Table 1). However, multiple blood cultures demonstrated negative results, and the patient's hemodynamics had been stabilized. Therefore, sepsis-associated disseminated intravascular coagulation was deemed unlikely, as was sepsis-related AKI. The transient abnormal coagulation profile may have been due to the preceding multiple invasive procedures and was presumably exacerbated by the patient's limited hepatic functional reserve because of chronic congestive liver.

Unfortunately, we did not consider the AKI to be quetiapine-related initially, as we knew that the liver was the primary route of metabolism and other drugs that could induce AKI were also used in the intensive-care setting. We also increased the dose of quetiapine during the course of AKI, as it seemed to be effective for the treatment of his mental instability. These factors may have delayed the diagnosis. The clearance of quetiapine is reduced with aging and hepatic dysfunction (2). The risk of drug-induced ATN depends on the total dose of the relevant drug (10). Given that our case involved an elderly patient with hepatic dysfunction, the clearance of quetiapine was likely low, which may have consequently resulted in a relatively high serum level

of quetiapine, leading to the observed AKI. The side effects may have been exacerbated by significant hypoalbuminemia due to possibly elevated levels of free unmetabolized quetiapine (11). Furthermore, quetiapine is metabolized by the liver with cytochrome P450 3A4. In the present case, benidipine and tolvaptan would have interacted with quetiapine, as they are metabolized with the same enzyme. We deem these combined etiologies and conditions likely to have helped worsen the progression of quetiapine-related AKI, which ultimately required CHDF. No data have been obtained regarding the clinical effect of CHDF on the clearance of quetiapine from human blood. However, given the distribution volume and protein binding ratio of quetiapine, the clearance rate by a single hemodialysis session was calculated to be 0.8% (12), supporting the notion that CHDF in the current case was unlikely to have helped remove quetiapine from the blood. The further accumulation of cases and molecular and pharmacokinetic studies is necessary to elucidate the detailed pharmacological mechanisms involved in quetiapine-related AKI.

In conclusion, considering the frequent use of quetiapine for delirium in elderly patients in intensive-care settings, this case highlights the potential risk of quetiapine-related AKI, or more specifically, ATN. Close consultation with the Psychiatry Department for the careful adjustment of the initial and subsequent doses is necessary, taking into consideration each patient's background and general condition.

The authors state that they have no Conflict of Interest (COI).

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References

1. Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. Ann Intern Med **161**: 242-248, 2014.
2. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet **40**: 509-522, 2001.
3. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract **120**: c179-c184, 2012.
4. Zhao A, Tan M, Maung A, Salifu M, Mallappallil M. Rhabdomyolysis and acute kidney injury requiring dialysis as a result of concomitant use of atypical neuroleptics and synthetic cannabinoids. Case Rep Nephrol **2015**: 235982, 2015.
5. Huynh M, Chee K, Lau DH. Thrombotic thrombocytopenic purpura associated with quetiapine. Ann Pharmacother **39**: 1346-1348, 2005.
6. Ceri M, Unverdi S, Altay M, Duranay M. Comment on: low-dose quetiapine-induced severe rhabdomyolysis. Ren Fail **33**: 463-464, 2011.
7. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med **36**: S216-S223, 2008.
8. Baldwin DS, Levine BB, McCluskey RT, Gallo GR. Renal failure and interstitial nephritis due to penicillin and methicillin. N Engl J Med **279**: 1245-1252, 1968.
9. Perazella MA. Diagnosing drug-induced AIN in the hospitalized patient: a challenge for the clinician. Clin Nephrol **81**: 381-388, 2014.
10. Markowitz GS, Perazella MA. Drug-induced renal failure: a focus on tubulointerstitial disease. Clin Chim Acta **351**: 31-47, 2005.
11. Wada K. Clinical issues on prescribing psychotropics for elderly patients. Seishin Shinkeigaku Zasshi **114**: 719-725, 2012 (in Japanese, Abstract in English).
12. Ohno Y, Yamamoto T, Hisaka A, Suzuki H. Touseki Kanja eno Touyo no Hyouka. The Pharmaceuticals Monthly **51**: 93-97, 2009 (in Japanese).