



Three Cases of Hemodialysis Patients Receiving High-Dose Ceftriaxone: Serum Concentrations and Its Neurotoxicity

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INTRODUCTION

Ceftriaxone (CTRX) is a third-generation cephalosporin widely used to treat common infections such as pneumonia and urinary tract infections.¹ The therapeutic dose is usually 1 to 2 g/d administered i.v. and can be increased up to 4 g/d for severe infections. Because CTRX is excreted via the biliary and the urine, patients with renal failure require no adjustment in dosage.² However, in cases of end-stage renal disease (ESRD), dose reduction of CTRX is recommended because of delayed clearance.^{3,4} Recently, it has been reported that CTRX showed severe neurotoxicity in patients with ESRD or renal insufficiency, but no reports have discussed the association between the serum concentration of CTRX and its neurotoxicity.^{5–9} Here, we report 3 cases of ESRD patients administered high-dose CTRX; 2 patients showed neurotoxicity, whereas the other patient showed no side effects. We measured serum concentrations of CTRX in these 3 patients and reviewed the relationship between CTRX serum concentration and neurotoxicity.

CASE PRESENTATION

Case 1

A 72-year-old man undergoing hemodialysis was admitted to our hospital because of pneumonia (day 1). His past medical history included myocardial infarction, ischemic stroke, and ESRD due to diabetic nephropathy accompanied with membranous nephropathy. CTRX was administered at a dose of 4 g/d for 7 days (days 1–7) and 2 g/d for 3 days (days 8–10). On day 8, his consciousness became impaired. He was clinically diagnosed with delirium and was prescribed haloperidol, which improved his symptoms. However, his consciousness

deteriorated to a Glasgow Coma Scale (GCS) score of 11 points (E4V3M4), and his legs moved spasmodically early in the morning of day 12 (Figure 1). Vital signs and physical examinations showed no special findings. A neurological evaluation found Babinski reflexes and myoclonic movements in both legs. Laboratory data and head computed tomography revealed no abnormal findings for impaired consciousness. Electroencephalography showed diffuse slow-wave activity but no sharp wave activity indicating epilepsy. On day 13, the patient's consciousness improved gradually, and he fully recovered on day 14. Later, we found that the serum concentration of CTRX on day 8 was very high (472 µg/ml; trough value), which was indicative of CTRX-induced neurotoxicity.

Case 2

A 75-year-old woman undergoing hemodialysis was admitted to our hospital due to diverticulitis (day 1). Her past medical history included myelodysplastic syndrome, atrial fibrillation, and ESRD due to chronic pyelonephritis. CTRX was administered at a dose of 2 g/d for 9 days (days 1–9). She had developed acute liver injury on day 4 due to drug-induced hepatopathy. On day 9, she presented with agitation, hyperkinesia, and confused conversations. Head CT and MRI revealed no significant findings. EEG showed diffuse slow-wave activity. Since CTRX-induced neurotoxicity was suspected, its administration was discontinued. Her consciousness had a GCS score of 14 points (E4V4M6) on day 9, and it further deteriorated to 7 points (E1V2M4) on day 11. On day 13, her impaired consciousness gradually improved (Figure 2). Serum concentrations of CTRX on days 4, 6, and 9 were 304 µg/ml, 331 µg/ml, and 422 µg/ml, respectively, at the trough values.

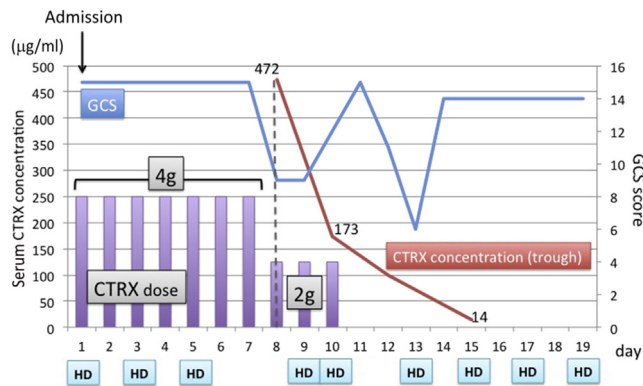


Figure 1. Clinical course of case 1. CTRX, ceftriaxone; GCS, Glasgow Coma Scale; HD, hemodialysis.

Case 3

A 68-year-old woman undergoing hemodialysis was referred to our hospital because of pyogenic arthritis. Her past medical history included type 2 diabetes mellitus and ESRD due to diabetic nephropathy. CTRX at a dose of 4 g/d was administered for 7 days (days 1–7). Although no neurogenic symptoms developed at the time, we proposed dose reduction to her chief physician because of concern for CTRX neurotoxicity. From day 8, the amount of administered CTRX was reduced to 1 g/d, and the same dose was continued until day 23, when she was discharged. Serum concentrations of CTRX on days 2, 4, and 7 were 172 µg/ml, 178 µg/ml, and 188 µg/ml, respectively, at the trough values.

DISCUSSION

CTRX is an antibiotic that is widely used to treat common infections such as pneumonia and urinary tract infections.¹ As CTRX is excreted via both biliary and renal excretion, patients with renal failure require no adjustment in dosage.² However, in cases of ESRD, delayed clearance of CTRX has been reported.^{3,4} Simon *et al.*

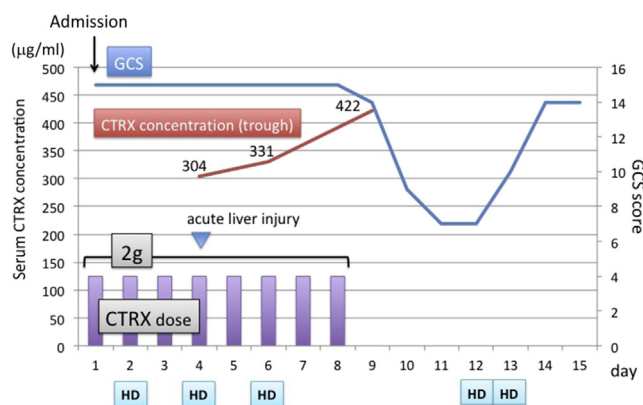


Figure 2. Clinical course of case 2. CTRX, ceftriaxone; GCS, Glasgow Coma Scale; HD, hemodialysis.

recommended CTRX 2 g i.v. after each dialysis session only in maintenance hemodialysis patients.⁴ We believe that CTRX accumulation in ESRD is not well recognized, as all attending doctors in our cases were not aware of it. In addition, The Sanford Guide to Antimicrobial Therapy does not mention dose reduction of CTRX in ESRD.¹⁰ To date, several cases of CTRX-induced neurotoxicity have been reported.^{5–9} All of these cases involved renal impairment, and half of the patients were on hemodialysis or peritoneal dialysis. Previous reports have shown that neurotoxicity manifestations occur between 1 and 10 days after CTRX administration but are improved 1 to 12 days after discontinuation. Clinical presentations, such as encephalopathy, mental status changes, myoclonus, choreoathetosis, and seizures, vary among patients. Grill and Maganti reported electroencephalographic findings in which there was diffuse slow-wave activity, semi-periodic triphasic sharp-wave activity, and frank periodic discharges.¹¹ The precise mechanisms of CTRX-induced neurotoxicity are not fully understood but are thought to be similar to those of other cephalosporins. These mechanisms include competitive antagonism of γ -amino butyric acid action¹² or direct cerebral toxicity through the induction of cytokines such as tumor necrosis factor- α .¹³ Risk factors extrapolated from patients with cephalosporin-induced neurotoxicity include advanced age, excessive dosage, renal insufficiency, and central nervous system disorders.⁶

In this report, we evaluated 3 cases of hemodialysis patients receiving high-dose CTRX. Figures 1 and 2 show the clinical courses of cases 1 and 2 with CTRX neurotoxicity. The trough values were assigned to the concentrations of CTRX in blood samples that were collected just before administration. In a previous report, when CTRX was administered 2 g twice daily to healthy adults, its peak and trough concentrations were 280 ± 39 µg/ml and 59 ± 21 µg/ml, respectively, on day 4.¹⁴ Our 2 case patients who presented with neurotoxicity had markedly high serum CTRX concentrations. Table 1 provides a summary of our 3 cases. There were significant differences among the serum concentrations and the clinical manifestations among these 3 cases. In patients 1 and 2, in whom neurotoxic effects were observed, the maximum trough values were very high, regardless of the administered dose. Although patient 3 was administered the same dose as patient 1, the trough values were not as high, and the patient did not show neurotoxicity. These results indicate that CTRX neurotoxicity correlates with serum concentration and not dosage.

Serum concentrations of CTRX in ESRD patients are regulated by various factors, the first of which is the ceftriaxone dose and the patient's physical condition.

Table 1. Patient profiles and clinical summary

Characteristic	Case 1	Case 2	Case 3
Age (yr), sex	72, Male	75, Female	68, Female
BW (kg), BMI (kg/m ²)	57.2, 22.6	53.7, 21.5	60.7, 23.7
Primary cause of ESRD	DM nephropathy, membranous nephropathy	Chronic pyelonephritis	DM nephropathy
Dialysis prescription	3.5 h HD dialyzer: 1.7 m ² /cellulose-triacetate Qb: 220 ml/min Qd: 500 ml/min	4 h HD dialyzer: 1.2 m ² /polysulphone Qb: 180 ml/min Qd: 500 ml/min	4 h HD dialyzer: 1.8 m ² /polysulphone Qb: 220 ml/min Qd: 500 ml/min
HD vintage	5 yr	14 yr	6 yr
Indication of CTRX	Pneumonia	Diverticulitis	Pyogenic arthritis
Dose of CTRX	Days 1–7: 4 g/d Days 8–10: 2 g/d	Days 1–9: 2 g/d	Days 1–7: 4 g/d Days 8–23: 1 g/d
Serum concentration of CTRX (trough)	472 µg/ml on day 8 173 µg/ml on day 10	304 µg/ml on day 4 331 µg/ml on day 6 422 µg/ml on day 9	172 µg/ml on day 2 178 µg/ml on day 4 188 µg/ml on day 7
Encephalopathy	+	+	–
Risk factors for CTRX encephalopathy	ESRD, CVD	ESRD	ESRD

BMI, body mass index; BW, body weight; CTRX, ceftriaxone; CVD, cerebrovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HD, hemodialysis; Qb, quantity of blood flow; Qd, quantity of dialysate flow.

Our patients' body mass indices were relatively small but were not significantly different from each other (Table 1). A CTRX dose of 4 g/d, 2 g/d, and 4 g/d was administered in cases 1, 2, and 3, respectively, but only case 1 and 2 showed neurotoxicity. This suggests that the administered dose was not directly related to neurotoxicity in our cases. A second factor regulating the serum concentration of CTRX is drug elimination. Of the total administered dose, 33% to 67% of CTRX is excreted in its unmetabolized form, whereas the remainder is secreted into the bile and is ultimately excreted in the feces as microbiologically inactive compounds.¹⁵ Our patients' hemodialysis vintages were between 5 and 14 years, and as the patients were almost anuric, CTRX may have mainly been excreted into the bile. In case 2, acute liver injury may have possibly led to higher CTRX concentrations compared with the other 2 cases. Furthermore, Nolin and Unruh have reported that in patients with ESRD, drug-metabolizing enzymes and transporters are affected and nonrenal drug clearance is impaired.¹⁶ The third factor is dialysis prescription. There is controversy as to whether CTRX is removed through hemodialysis; however, this may also depend on the dialyzer membranes. Gabutti *et al.* reported that polysulphone membranes were more permeable than cellulose membranes,¹⁷ which may have led to a decreased amount of CTRX that was extracted through the dialyzer membrane in case 1 of this study. As we reported herein, our 3 cases had different clinical manifestations. The difference in drug metabolisms and dialysis prescriptions may have accounted for the 3 different clinical courses.

In summary, we report a series of cases in which CTRX serum concentrations were measured; 2 of these

patients had CTRX neurotoxicity, and 1 patient was asymptomatic despite having received a high dose of CTRX on maintenance hemodialysis. The amount of administered CTRX dose cannot fully explain the large individual differences in neurotoxicity. We recommend stopping CTRX administration if a patient shows neurological symptoms, and subsequently checking the serum concentrations. Furthermore, to avoid the adverse effects of neurotoxicity, dose reduction is recommended when CTRX is administered to ESRD patients.

DISCLOSURE

All the authors declared no competing interests.

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