Importance and Reality of TDM for Antibiotics

Subjects: Infectious Diseases

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Under the Japanese health insurance system, medicines undergoing therapeutic drug monitoring (TDM) can be billed for medical fees if they meet the specified requirements. In Japan, TDM of vancomycin, teicoplanin, aminoglycosides, and voriconazole, which are used for the treatment of infectious diseases, is common practice. This means the levels of antibiotics are measured in-house using chromatography or other methods. In some facilities, the blood and/or tissue concentrations of other non-TDM drugs are measured by HPLC and are applied to treatment, which is necessary for personalized medicine.

HPLC TDM ceftriaxone daptomycin

1. Characteristics of Ceftriaxone (CTRX) and Significance of Therapeutic Drug Monitoring (TDM)

Ceftriaxone (CTRX) is a third-generation cephalosporin that has a broad antibacterial spectrum, good tissue migration, and a longer half-life than other cephalosporins, allowing for once-daily administration. CTRX has been used for a variety of indications and has many opportunities for use [1]. In addition, dose adjustment is not necessary for patients with impaired renal function [2]. Patel et al. reported that adjusting the dosage regimen of ceftriaxone for patients with impaired renal function should not be necessary when the daily dosage is 2 g or lower [3]. Antibiotic-associated encephalopathy (AAE) is a known side effect of cephalosporins. AAE is classified into three major categories: type I for cephalosporins and penicillins, type II for quinolones and macrolides, and type III for metronidazole; type I is said to be free of epileptic waves [4]. In particular, there have been many reports on AAE with cefepime (CFPM), a fourth-generation cephalosporin drug, including reports on the intoxication zone of blood levels responsible for AAE [5][6][7]. There are also scattered reports of AAE caused by CTRX, and according to an adverse drug reaction database study in France, the serious CNS adverse effects caused by CTRX and CFPM were reported to be similar [8]. AAE with CTRX has been reported more frequently in the elderly and patients with chronic kidney disease and is more likely to occur when high doses are given and blood and cerebrospinal fluid (CSF) concentrations are high [9][10][11].

In a recent report, Lacroix et al. [12] used the French pharmacovigilance database to analyze records of CNS adverse events due to CTRX that were recorded as occurring in 1995–2017. A total of 152 serious adverse drug reactions (ADRs) were analyzed: 112 resulted in hospitalization or prolonged hospitalization (73.7%), 12 resulted in death (7.9%), and 16 were life-threatening. The median age was 74.5 years, and the median rate of creatinine clearance (CLcr) was 35 mL/min. The median time of onset was 4 days; the mean daily dose was 1.7 g, with three patients receiving doses exceeding the maximum recommended dose; and plasma ceftriaxone levels were

recorded in 19 patients (12.5%), with eight patients exceeding the threshold for toxicity (>100 μg/mL). In addition, electroencephalography performed on 50 patients (32.9%) showed abnormalities in 37 (74%).

Although the frequency of CTRX-related encephalopathy in Japan is not clear, it has been reported that the sales volume of third-generation cephalosporins is about six times higher than that of fourth-generation cephalosporins [13], and caution is required.

2. Report on the Measurement of Blood Levels and Cerebrospinal Fluid (CSF) of CTRX in Japan

In Japan, researchers searched for clinically applied studies on CTRX that are not generally clinically measured. As a result, researchers present reports on the measurement of CTRX concentrations in cerebrospinal fluid by HPLC−UV in Japan.

Kotani et al. [14] measured CTRX concentrations in CSF samples collected from peritoneal dialysis patients diagnosed with CTRX-induced encephalopathy (CIE) using an HPLC–UV system to investigate whether high CTRX concentrations in CSF are associated with CIE. Their study used an octadecyl silica (ODS) column, methanol, and a mobile phase of mixed solution (25:75, *v*/*v*) in 10 mM phosphate to accurately analyze the CSF samples from CIE patients; the detection wavelength was 280 nm. Based on the current HPLC–UV capability, a linear range of 0.1–100 μg/mL (r = 0.999) was obtained. In a recovery study using a blank sample of human CSF and a control serum supplemented with CTRX, the recovery of CTRX was ≥95.3%, and the RSD was <5.8% (*n* = 3). CTRX in CSF and serum obtained from a patient diagnosed with CIE was measured using the developed HPLC–UV system. The concentration of CTRX in CSF and serum was 2.61 and 37.35 μg/mL, respectively. Researchers simulated the serum and CSF concentrations of CTRX using simulation software developed by Oda (**Figure 1**) [15].

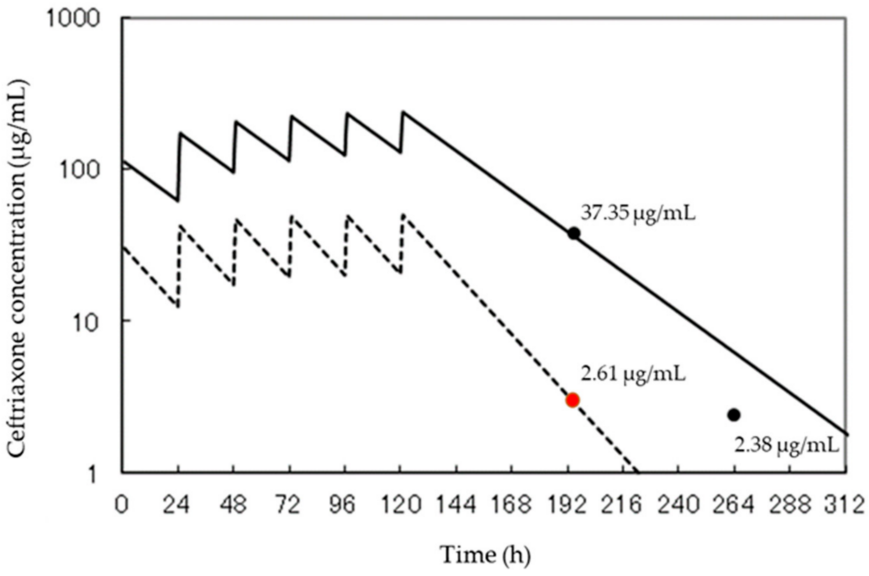


Figure 1. Simulation of blood concentration and human cerebrospinal fluid after ceftriaxone administration [14]. Researchers completed the

simulation ourselves using researchers' results. The solid line shows changes in blood concentration after ceftriaxone administration, and the dotted line shows changes in cerebrospinal fluid.

Suzuki et al. [16] reported the case of a patient with renal failure who experienced encephalopathy induced by CTRX. An 86-year-old woman undergoing maintenance hemodialysis was treated with CTRX for *Helicobacter cinaedi* bacteremia, and her mental status worsened during antibiotic administration. During the period when CTRX was administered at 2 g/day, the measured plasma and CSF CTRX concentrations were high (>100 and 10.2 µg/mL, respectively). The patient reported that her mental status improved after the antibiotic treatment was stopped. **Table 1** shows the PubMed search results for reports that measured blood and CSF concentrations of CTRX, DAP, LZD, and TZD in Japan.

Table 1. Summary of Japanese reports on serum and CSF concentrations of CTRX, DAP, LZD, and TZD [14][16][17][18][19][20][21][22][23][24][25][26][27][28][29].

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
CTRX	Age: 75 Sex: female	Development of HPLC method for accurate, precise, and selective determination of CTRX and its clinical application	peritoneal dialysis	2 g/day	HPLC-UV	-Chromatographic peak heights of CTRX: 0.1–100 µg/mL (r = 0.999) -Detection limit of CTRX: 35 ng/mL -Repeatability (*n* = 6) of the chromatographic peak height for 4.0 µg/mL CTRX: 0.38% RSD.-Recovery rates of CTRX: >95.3%, and these RSDs were <5.8%	37.35 µg/mL	2.61 µg/mL	[14]
	Age: 86 Sex: female	Report of encephalopathy associated with high levels of ceftriaxone in plasma and cerebrospinal fluid, investigation of the causal relationship between	hemodialysis	2 g/day	HPLC	nd	>100 µg/mL	10.2 µg/mL	[16]

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
		ceftriaxone administration and the development of encephalopathy							
	Population: *n* = 43 patients Sex: male median age: 51.7 years (IQR 33.3–67.1) median BMI: 24.7 kg/m^2 (IQR 22.4–27.7 kg/m^2)	Determining the role of transporter genetic variation and blood-brain barrier permeability in predicting ceftriaxone exposure in the central nervous system	estimated creatinine clearance < 30 mL/min	2 g twice a day	HPLC	-Detection limits: 0.24 mg/L in plasma and 0.5 mg/L in CSF -Accuracy: 5.2% for plasma, 7.2% for CSF -Intra- and inter-day coefficients of variation (CV%): 3.6% and 4.5% for plasma samples, and 7.2%, 7.8%, and 10.3% for CSF samples -Recovery rate: 86% (CV% = 3) for CSF samples and 82% (CV% = 8) for plasma samples.	Median Cmax: 157,193.00 ng/mL (IQR 105,164.0–184,852.0 ng/mL)	Median Cmax: 3512.0 ng/mL (IQR 2134.0–6193.0 ng/mL)	[17]
	Population: *n* = 16 patients	Evaluation of tolerability and pharmacokinetic parameters of high-dose ceftriaxone in adult patients treated for central nervous system infections: pharmacological data from two French cohorts	nd	6.5 g/day (range 4–9 g) 97.5 mg/kg (range 77–131 mg/kg)	HPLC	nd	Median total plasma: 69.3 mg/L (range 21.6–201.3 mg/L; *n* =14) Median unbound plasma: 7.95 mg/L (range 0.8–43.7 mg/L; *n* = 8)	Median: 13.3 mg/L (range 0.9–91.2 mg/L)	[18]
	Population: *n* = 7 patients	Investigation of the pharmacokinetics ofboth antibiotics in patients with non-inflammatory	Scr < 1.5 mg/dL	2 g single dose 30 min	HPLC-UV	-Quantification limits of ceftriaxone; 0.8 mg/L in serum and 0.08 mg/L in CSF. -Interday	Cmax: 172.2–271.7 mg/L (median = 249.6; *n* = 6)	Cmax: 0.18–1.04 mg/L (median = 0.43; *n* = 5), confirmed 1–16 h after injection	[19]

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
		obstructive hydrocephalus undergoing external ventricular surgery treated with cefotaxime or ceftriaxone for extracerebral infections				coefficients of variation; 2.0% 249.6; *n* = 6) at 99.7 and 6.8% at 1.55 mg/L inserum and 3.3% at 16.2 and 6.4% at 0.16 mg/L in CSF (*n* = 6).		(median = 12 h; *n* = 5).	
DAP	Population:16 patients (8 males and 8 females) Age: 70.0 ± 3.4 years weight: 47.6 ± 5.0 kg	Investigate the optimal dosing regimen for daptomycin and determine the need and appropriateness of a high-dose regimen in terms of PK / PD parameters using Monte Carlo Simulation and TDM in a Japanese clinical setting	CLcr 16.2–173.4 mL/min (*n* = 11) hemodialysis (*n* = 5)	single doses (6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg) and dosing intervals (24 h and 48 h)	HPLC-UV	-Lowest limit of quantification: 0.78 µg/mL	Cmin: 0.13–49.4 µg/mL Cpeak: 34.2–130.0 µg/mL	nd	[20]
	Population: *n* = 20 patients	Investigate associations between DAP Cmin and creatine phosphokinase elevation via logistic regression analysis (E/R analysis), and to analyze DAP PPK via adaptation of a one-compartment model in Japanese patients to determine optimal DAP doses for minimizing adverse effects	CLcr 22.4–213.8 mL/min,	2.8–8.6 mg/kg	HPLC-UV	-Lowest limit of quantitation: 1.0 µg/mL -within-day and between-day coefficients of variation of <5.0%.	Cmin: 2.8–92.4 µg/mL Cpeak: 30.4–76.7 µg/mL	nd	[21]

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
		and maximizing treatment success by E/R analysis.							
	Population: *n* = 15 patients	Development of an assay method for the determination of total and free daptomycin in human plasma	nd	4–8 mg/kg once over a 24-hour period.	LC-MS/MS	-Concentration ranges: 1.0–100 µg/mL in total daptomycin and 0.1–10 µg/mL in free daptomycin - Limits of quantitation: 1.0 µg/mL(total daptomycin) and 0.1 µg/mL(free daptomycin) -Recovery rate: total daptomycin measurements ranged from 106.1% and free daptomycin measurements ranged from 98.2%	The plasma concentration ranges of total and free daptomycin in 15 infected patients were 3.01–34.1 and 0.39–3.64 µg/mL	nd	[22]
	Population: two patients admitted to intensive care unit (2 males) Weight: 61.1 kg, 59.0 kg	Development of a new assay for measuring total and free concentrations of daptomycin in plasma with potential clinical applications	CLcr 17.5 mL/min CLcr 140.5 mL/min	-every 48 h of 350 mg (CLcr < 30 mL/min)- once-daily dose of 350 mg (CLcr ≥ 30 mL/min)	UPLC-MS / MS	-Concentration ranges: 0.5–200 µg/mL in total daptomycin and 0.04–40 µg/mL in free daptomycin- Recovery rate: approximately 100% of free daptomycin from ultrafiltration -Limits of quantitation: 0.5 µg/mL (total daptomycin) and 0.04 µg/mL (free daptomycin) -Recovery rate: total daptomycin measurements ranged from 57.1 to 67.4% and	-Patient with low renal function: Cmax of free drug: 2.85 µg/mL (Day 3), 4.2 µg/mL (Day 5) Ctrough of free drug: 0.29 µg/mL (Day 3), 0.86 µg/mL (Day 5) -Patient with normal renal function: Median unbound plasma: Cmax of free drug: 2.69 µg/mL (Day 3), 2.77	nd	[23]

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
						free daptomycin measurements ranged from 54.6 to 62.3%	µg/mL (Day 5) Ctrough of free drug: 0.77 µg/mL (Day 3), 0.34 µg/mL (Day 5)		
	Population: *n* = 53 patients Sex: Male (*n* = 33), female (*n* = 19)	Examine serum daptomycin levels, creatinine phosphokinase levels, and the incidence of other adverse effects	CLcr ≥ 80 mL/min: *n* = 15 30 ≤ CLcr < 80 mL/min: *n* = 23 CLcr < 30 mL/min: *n* = 14 haemodialysis: *n* = 8	4.0 < dose ≤5.0 mg/kg: *n* = 7 5.0 < dose ≤6.0 mg/kg: *n* = 19 6.0 < dose ≤7.0 mg/kg: *n* = 17 ≤7.0 mg/kg: *n* = 4	HPLC-PDA	-Response at the lowest concentration (3.5 µg/mL) was significantly more than 5 times higher than that of the blank serum -Interday coefficient of variation for the lowest and highest concentration (200 µg/mL) samples was within 15%.	Cmax: 172.2–271.7 mg/L (median = 249.6; *n* = 6)	nd	[24]
LZD	Age: 78 Sex: male weight: 48.2 kg	Treatment of mediastinitis with TDM of serum and wound exudate concentrations of linezolid in renal function impaired patients.	Scr: 5.6 mg/dL glomerular filtration rate: 8.6 mL/min/1.73 m^2	600 mg every 24 h After that, 300 mg every 24 h	HPLC	-Lower limit: 0.1 µg/mL -Intra/interday precision below 5.0%	Cmin: 11.5 µg/mL (Day 21) Cmin: 5.5 µg/mL (Day 55)	nd	[25]
	Age: 77 Sex: female weight: 55 kg	TDM was effective in preventing thrombocytopenia with linezolid: a case report	CLcr 29.9 mL/min	600 mg twice a day After that, 600 mg every 24 h	HPLC	-Lower limit: 0.25 µg/mL -Intra/interday precision below 5.0%	39.4 µg/mL (Day 9)	nd	[26]
	Age: 79 Sex: female weight: 58.5 kg	Successful combination therapy with linezolid and rifampicin with appropriate management of	Scr 0.4 mg/dL	600 mg twice a day Thereafter, 300 mg twice a day	HPLC	-Lower limit: 0.1 µg/mL -Intra/interday precision below 5.0%	Cmin: 15.1 µg/mL (Day 5) Cmin: 13.9 µg/mL (Day 8) As a result of combination therapy, Cmin	nd	[27]

HPLC:high performance liquid chromatography; HPLC-UV:high performance liquid chromatography with ultraviolet detection; Scr:serum creatinine; CSF: cerebrospinal fluid; IQR:interquartile range; RSD: relative standard deviation; nd: not described; LC-MS/MS:Liquid Chromatograph-tandem Mass Spectrometer; UPLC-MS/MS:ultra-performance liquid chromatography coupled to tandem mass spectrometry; HPLC-PDA:high-performance liquid chromatography equipped with photodiode array; CLcr:creatinine clearance; MRSA: methicillin resistant Staphylococcus aureus; UHPLC-MS/MS:ultra-high-performance liquid chromatography coupled with tandem mass spectrometry.

In Japan, the measurement of the CTRX blood concentration is not covered by insurance and is limited to facilities with appropriate laboratory equipment. In practice, there is a time lag between collecting samples and obtaining

Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
		linezolid TDM in MRSA osteomyelitis: a case report		At the time rifampicin is combined, 600 mg twice a day			was in the optimal range of 3.7 to 7.2 mg/mL.		
TZD	Population: *n* = 3 patients	Development of an assay system for simultaneous quantification of plasma concentrations of LZD, DAP, and TZD and its clinical application	CLcr 48.3–64.5 mL/min	200 mg once daily	UPLC-MS/MS	-TZD showed good linearity over wide ranges of 5–5000 ng/mL. -The lower limited of quantification and three quality controls (QCs: low, medium and high) were less than 15% for both accu-racy and precision. -Recovery rate of TZD: more than 84.8%	Cpeak and Cmin of TZD ranged from 1.87 to 4.92 μg/mL and from 0.09 to 0.78 μg/mL	nd	[28]
	Population: *n* = 3 patients	Development of an assay for simultaneous quantification of 12 antimicrobial agents commonly used in ICU and its clinical application	CLcr 51.7–60.4 mL/min	200 mg once daily	UHPLC-MS/MS	-The concentration ranges of calibration curves for TZD was 0.01–5 μg/mL. -The measured concentrations in blanks were less than 20% of the peak response of the lower limited of quantification and less than 5% for internal standard	The ranges of Cmin and Cpeak in patients with CLcr of 51.7–60.4 mL/min were 0.06–0.12 and 2.67–4.01 μg/mL	nd	[29]
LZD	Age: 78 Sex: male weight: 48.2 kg	Treatment of mediastinitis with TDM of serum and wound exudate	Scr: 5.6 mg/dL glomerular filtration rate: 8.6	600 mg every 24 h After that, 300 mg every 24 h	HPLC	-Lower limit: 0.1 μg/mL -Intra/interday precision below 5.0%	Cmin: 11.5 μg/mL (Day 21) Cmin: 5.5	nd	[25]

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Drug	Characteristics	Objective	Renal Function	Dose	Measurement System	Measurement Accuracy	Blood Concentration	CSF Concentration	Ref.
		concentrations of linezolid in renal function impaired patients.	mL/min/1.73 m^2				µg/mL (Day 55)		
	Age: 77 Sex: female weight: 55 kg	TDM was effective in preventing thrombocytopenia with linezolid: a case report	CLcr 29.9 mL/min	600 mg twice a day After that, 600 mg every 24 h	HPLC	-Lower limit: 0.25 µg/mL -Intra/interday precision below 5.0%	39.4 µg/mL (Day 9)	nd	[26]
	Age: 79 Sex: female weight: 58.5 kg	Successful combination therapy with linezolid and rifampicin with appropriate management of linezolid TDM in MRSA osteomyelitis: a case report	Scr 0.4 mg/dL	600 mg twice a day Thereafter, 300 mg twice a day At the time rifampicin is combined, 600 mg twice a day	HPLC	-Lower limit: 0.1 µg/mL -Intra/interday precision below 5.0%	Cmin: 15.1 µg/mL (Day 5) Cmin: 13.9 µg/mL (Day 8) As a result of combination therapy, Cmin was in the optimal range of 3.7 to 7.2 mg/mL.	nd	[27]
TZD									
	Population: *n* = 3 patients	Development of an assay system for simultaneous quantification of plasma concentrations of LZD, DAP, and TZD and its clinical application	CLcr 48.3–64.5 mL/min	200 mg once daily	UPLC-MS/MS	-TZD showed good linearity over wide ranges of 5–5000 ng/mL. -The lower limited of quantification and three quality controls (QCs: low, medium and high) were less than 15% for both accu-racy and precision. -Recovery rate of TZD: more than 84.8%	Cpeak and Cmin of TZD ranged from 1.87 to 4.92 µg/mL and from 0.09 to 0.78 µg/mL	nd	[28]
	Population: *n* = 3 patients	Development of an assay for simultaneous quantification of	CLcr 51.7–60.4 mL/min	200 mg once daily	UHPLC-MS/MS	-The concentration ranges of calibration	The ranges of Cmin and Cpeak in patients with	nd	[29]

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		12 antimicrobial agents commonly used in ICU and its clinical application				curves for TZD was 0.01–5 μg/mL. -The measured concentrations in blanks were less than 20% of the peak response of the lower limited of quantification and less than 5% for internal standard	CLcr of 51.7–60.4 mL/min were 0.06–0.12 and 2.67–4.01 μg/mL		

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