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CASE SERIES

Intrathecal or Intraventricular Tigecycline Therapy for Central Nervous System Infection Associated with Carbapenem-Resistant *Klebsiella pneumoniae*

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Purpose: Infection with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a great challenge. Central nervous system (CNS) infection caused by CRKP is rarely reported, and effective treatment is limited. Thus, this study aimed to assess intrathecal (IT) or intraventricular (IVT) injection of tigecycline for clearing infection with CRKP in CNS.

Patients and Methods: Two patients who had intracranial infection with CRKP after craniotomy were treated in our institution and analyzed retrospectively, summarizing their therapeutic schedules.

Results: They all had a fever with the positive results of cerebrospinal fluid (CSF) test, and CSF culture showed positive for CPKP, which was sensitive only to tigecycline. In addition, the MIC of polymyxin B was not tested due to the limited laboratory conditions. After IT or IVT injection of tigecycline treatment, the temperature of the patients became normal in 3 days, with normal levels of white blood cells, protein, glucose and chlorine concentrations in the CSF. Crucially, twice CSF cultures also became negative with no clinical symptoms of intracranial infection after IT or IVT injection of tigecycline treatment. Moreover, there were no adverse drug reactions observed.

Conclusion: IT or IVT injection of tigecycline may be a bright choice to control intracranial infection with CRKP.

Keywords: central nervous system infection, CNS, carbapenem-resistant *Klebsiella pneumoniae*, CRKP, tigecycline, treatment

Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has became a global threat in recent years, with high mortality associated with CRKP infection.[1] It was reported that the mortality rates are as high as 33.24%, 46.71%, 50.06% and 44.82%, in North America, South America, Europe and Asia, respectively.[2] Central nervous system (CNS) infection is one of the most severe complications of neurosurgery, and significantly aggravates the primary disease, especially healthcare-related meningitis and ventriculitis which were caused by CRKP.[3] Tigecycline is one of the most important drugs for the treatment of CRKP infections.[4] Previous reports mainly studied the effect of tigecycline on pulmonary infection, and skin and soft tissue infection, etc, only a few studies investigated the effect of tigecycline on CNS infection caused by *Acinetobacter baumannii*.[5,6] Up to now, the effect of the drug on CRKP infections in CNS was rare reported.[7]

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Herein, we reported two cases infected with CRKP in the CNS, who were cured by intrathecal (IT) or intraventricular (IVT) injection of tigecycline.

At present, rare relevant research has been reported yet on IT or IVT injection of tigecycline for treating CNS infections with CRKP.[7]

Case Presentation

Case 1: A female patient, 43 years old, had undergone removal of intracranial hematoma and decompressive craniectomy because of traffic accident. Ten days after the surgery (D10), she had a high fever of 39.5 °C, the blood test was performed immediately and the results showed white blood cells (WBC) were as high as 14.11×10^9/L with the proportion of neutrophils as high as 88%. Meanwhile, we performed lumbar puncture for her and the cerebrospinal fluid (CSF) was tested immediately. The results of CSF test revealed high WBC counts and protein concentration and low concentrations of glucose (Table 1). After 2 days, CRKP was reported form patients' CSF cultures. Disk diffusion method was used for the susceptibility test of tigecycline because of the limited laboratory conditions. The results showed it was sensitive only to tigecycline with bacteriostatic circle of 19 mm (Table 2).[8] Due to the limited laboratory conditions, the MIC of polymyxin B was not tested. But the blood culture was negative. Intracranial infection was diagnosed and meropenem (2g q8h IV) and tigecycline (50 mg q12h IV, loading dose 100mg) were administered intravenously combined with IT injection of tigecycline (2.5 mg q12h) for 14 days. On D20 and D26, results of CSF tests from repeated lumbar puncture returned to normal, and she recovered from fever and clinical symptoms of intracranial infection (Table 1). Therefore, we discontinued the antimicrobials. During the treatment period, she was effectively and safely treated without nephrotoxicity or seizures. Seven days later (D33), all of the therapies was stopped, and the patient recovered and discharged.

Case 2: A male patient, 57 years old, was diagnosed with left frontal lobe contusion, left cerebellar contusion and subarachnoid hemorrhage because of traffic accident. Initially, we performed conservative treatment for him. On D3, computed tomography (CT) showed aggravation of left cerebral edema accompanied by diminished consciousness. Immediately, we placed a left ventricular drainage tube for him. From D15, he began to have fever with slightly turbid CSF. On D17, the temperature rose to 39°C. CSF test revealed WBC counts as high as 470×10^6/L, with high concentration of total protein and low glucose content of 1.7 mmol/L (Table 3). On D19, CSF culture indicated CRKP. We used disk diffusion method to test the susceptibility of tigecycline, and showed CRKP was sensitive to tigecycline with bacteriostatic circle of 19 mm (Table 4).[8] MIC of polymyxin B was not tested because of the same reason mentioned above. Meanwhile, the blood microbial culture was negative. The patient was administered immediately with meropenem (2 g q8h IV) and tigecycline (50 mg q12h IV). However, his body temperature was still as high as 39°C for 3 days. Repeated analysis of CSF showed significantly abnormal results (Table 3). D24, repeated CSF test showed WBC count of 416×10^6/L, with high rate total protein of 1641 mg/L and glucose of 1.5 mmol/L (Table 3). On D25, CSF culture showed CRKP with the same drug sensitivity as before. Then, we stopped intravenous drip of tigecycline and used IVT injection of tigecycline (2.5 mg q12h) instead. Regimen of meropenem (2 g q8h IV) remained unchanged. The therapeutic schedule of IVT tigecycline was instituted with permission from members of the patient's family. Seven days after the treatment (D32), the patient's results of CSF test improved and the left ventricular drainage fluid became clear gradually (Table 3). On D39, the temperature, clinical symptoms and laboratory tests of CSF returned to normal (Table 3). More importantly, CSF culture got negative for three consecutive times. Therefore, we discontinued the antimicrobial therapy and the left ventricular drainage tube

Table 1 CSF Test Results (Case 1)

	Before IT Tigecycline Treatment (D10)	Post-IT Tigecycline Treatment (D26)
WBC ($\times10^6$/L)	200	3
Protein (mg/L)	671	187
Glucose (mmol/L)	2.26	3

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.

Table 2 Antibiotic Susceptibility Tests for *Klebsiella pneumoniae* in CSF of Case 1

Antibiotics	Method	MIC (μg/mL)	Susceptibility
Amikacin	MIC	≥32	R
Cefuroxime sodium	MIC	≥64	R
Cefoxitin	MIC	≥64	R
Ceftazidime	MIC	≥64	R
Cefepime	MIC	≥32	R
Cefoperazone/sulbactam	MIC	≥64	R
Imipenem	MIC	≥16	R
Levofloxacin	MIC	≥8	R
Meropenem	MIC	≥16	R
Piperacillin tazobactam	MIC	≥128	R
Ciprofloxacin	MIC	≥4	R
Compound sulfamethoxazole	MIC	≥320	R
Tigecycline	K-B	19mm[a]	S

Note: [a]Antibacterial circle diameter.
Abbreviations: CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration; K-B, Kirby–Bauer; S, susceptible; R, resistant.

Table 3 CSF Test Results (Case 2)

	Before IV Tigecycline Treatment (D17)	Post IV Tigecycline Treatment (D22)	Before IVT Tigecycline Treatment (D24)	Post-IVT Tigecycline Treatment (D32)	Post-IVT Tigecycline Treatment (D39)
WBC ($\times 10^6$/L)	470	460	416	240	10
Protein (mg/L)	1099	929	1641	409	344
Glucose (mmol/L)	1.7	1.6	1.5	2.3	2.7

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.

was removed. The patient recovered and discharged 1 week later. There were no adverse drug reactions observed during IVT injection of tigecycline.

Discussion

The spread of CRKP infection has become a worldwide challenge. It was reported that the mortality rate of CRKP infection is as high as 40% to 50%.[9] In addition, rapid growth of bacterial resistance to imipenem and meropenem was found in recent years according to the CHINET data, because of the widespread use of carbapenems. The antibiotics for CNS infections with CRKP are very limited. Intracranial infections caused by Gram-negative bacilli have shown a significant upward trend in recent years.[10] Based on the CHINET data published in 2020, *Klebsiella pneumonia* is one of the top five bacteria responsible for CSF infection.[10] Intracranial infection of

Table 4 Antibiotic Susceptibility Tests for *Klebsiella pneumoniae* in CSF of Case 2

Antibiotics	Method	MIC (μg/mL)	Susceptibility
Amikacin	MIC	≥32	R
Cefuroxime sodium	MIC	≥64	R
Cefoxitin	MIC	≥64	R
Ceftazidime	MIC	≥64	R
Cefepime	MIC	≥32	R
Cefoperazone/sulbactam	MIC	≥64	R
Imipenem	MIC	≥16	R
Levofloxacin	MIC	≥8	R
Meropenem	MIC	≥16	R
Piperacillin tazobactam	MIC	≥128	R
Ciprofloxacin	MIC	≥4	R
Compound sulfamethoxazole	MIC	≥320	R
Tigecycline	K-B	19mm[a]	S

Note: [a]Antibacterial circle diameter.
Abbreviations: CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration; K-B, Kirby–Bauer; S, susceptible; R, resistant.

CRKP using IT or IVT tigecycline therapy was rarely reported so far. Here, we report the curative effect of intracranial tigecycline on the CNS infections caused by CRKP, through two cases.

Polymyxin B and tigecycline are now regarded as the last-line antibiotics especially for XDR gram-negative bacillus infections. However, it is difficult to penetrate into the brain for polymyxin B, unless intrathecally injected. However, intrathecally injection of polymyxin B could lead to high incidence of nephrological and neurological side effects. As reported previously, approximately 6–54% of the patients develop drug-related nephrotoxicity.[11,12] Besides, polymyxins are associated with side effects including peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and even neuromuscular blockade, which could lead to respiratory failure, even apnea. Other neurologic adverse reactions include psychosis, coma, convulsion, ptosis, diplopia, areflexia, dysphagia, and dysphonia, etc.[13,14] These neurotoxicities are easily confused with the clinical symptoms found in patients with brain trauma, which increased difficulties in clinical differential diagnosis. Polymyxin B could even induce skin hyperpigmentation as reported by our previous study.[15] Studies show that colistin might affect mitochondrial functions of nerve tissues, which induce mitochondrial dysfunction of nervous cells in mice.[16] Further study demonstrated that polymyxin-induced neurotoxicity in neuroblastoma-2a (N2a) cells is related to inflammatory response partly regulated by IL-1β/p-IκB-α/NF-κB pathways.[17] Due to the serious nephrological and neurological side effects of polymyxins and the drug was not available in the hospital, we are more preferred to use tigecycline for the treatment of XDR-bacterial infections for these two cases.

Tigecycline is a broad-spectrum antibiotic that inhibits gram-positive, gram-negative, and anaerobic bacteria that were common strains in CNS infections.[18] In Europe and the United States, it had been approved for the treatment of complicated skin and skin structure infections as well as complicated intra-abdominal infection (cIAI).[19] It has a favorable nervous system toxicity compared with polymyxin B.[20] However, tigecycline hardly reaches the MIC in brain due to low penetration into blood–brain barrier (BBB).[21] Compared with the plasma levels of tigecycline, the concentration is only 11% in the brain.[20,22] Another study showed that the peak level of tigecycline in the CSF could reach 41% of plasma levels in patients with meningitis. Even then, at a dose of 50 mg q12h, the concentration is still too low for efficient treatment of meningitis.[23] Additionally, tigecycline is a bacteriostatic agent. Considering the severity of CRKP intracranial infection and its poor prognosis above mentioned, we

decided to use IT or IVT tigecycline for treatment of CRKP in CNS. We deemed that IT or IVT tigecycline was the main reason for the successful cure of the two patients. Hence, IT or IVT may be a potential method to cure CRKP intracranial infection.

The dose and the length of IT or IVT tigecycline is another key we have to consider. It has been reported that intrathecal or intraventricular tigecycline is effective on intracranial infection with multidrug-resistant *Acinetobacter baumannii, Klebsiella pneumonia*, and vancomycin-resistant *Enterococci*. These papers showed several treatment options for reference[6,24–37] (Table 5). In these literatures, IT, IVT or continuous ventricular irrigation (CVI) of tigecycline was used for treating intracranial infection in adults and infants. Lauretti et al firstly reported IVT tigecycline for treatment of meningitis by XDR-*Acinetobacter baumannii* in 2017. Till now, there were only three papers on successful treatment of IVT tigecycline for treating XDR-*Klebsiella pneumonia* CNS infection, two for adults and one for infant. In our present study, besides IVT tigecycline, we also reported a successful experience of IT tigecycline for the treatment of CNS CRKP infection, for the first time. The dosage of intravenous injection commonly ranged from 50 mg to 100 mg twice daily in the label and literatures. The IT, IVT, or CVI dose of 2–20 mg/day was successfully used in adult and pediatric cases without any toxicity. The length of therapy was between 12 days and 78 days (Table 3). In our cases, the patients had undergone surgery operation and resulted in CNS infection with CRKP. In addition, the sensitive of the CRKP is poor, only sensitive to tigecycline. Finally, IT or IVT injection of 2.5 mg of tigecycline was administered twice a day for 14 days, based on the literature reports and the characteristics of pharmacokinetics and pharmacodynamics of tigecycline. Consequently, the temperature, routine tests and biochemistry indicators of the CSF were normal. Repeated CSF cultures were all negative after IT or IVT tigecycline treatment, and there were no side effects observed.

Table 5 Administration of Tigecycline in the Literatures

Reference	Age/Sex	Diagnosis	Strain	IV/CVI/ IT/IVT Tigecycline	Days to CSF Sterilization	Toxicity	Infection Outcome	Survival
[6]	17/Male	Meningitis	*Acinetobacter baumannii*	IV,47.5mg q12h; IVT,4mg q12h; IT,4 mg q24h	40	None	Cured	Yes
[24]	67/Male	Meningitis	*Klebsiella pneumonia*	IV, 49 mg q12h IVT, 1 mg q12h IV, 45 mg q12h IVT, 5 mg q12 h IV, 40 mg q12h IVT, 10 mg q12h	78	None	Cured	Yes
[25]	Five-month/ Female	Central nervous system infections	Daptomycin-resistant VRE *faecium*	IV,1.2 mg/kg q12h IVT, 4 mg q24h	20	None	Cured	Yes
[26]	NR	Central nervous system infection	*Acinetobacter baumannii*	IV,50 mg q12h (after a loading dose of 100 mg); IT,10 mg q12h	14	None	Cured	Yes
[27]	55/Male	Meningitis	*Acinetobacter baumannii*	IV,100 mg q12h CVI,10mg q12h IV,50 mg q12h IVT, 2 mg q12h	17	None	Cured	Yes
[28]	50/Male	Intracranial infection	*Acinetobacter baumannii*	IV, 100 mg q12h IVT, 3 mg q12h IVT, 4 mg q12h	12	None	Cured	Yes
[29]	22/ Male	Meningitis	*Acinetobacter baumannii*	IV, 100 mg q12h IVT, 2 mg q24h IVT, 2mg q12h	75	None	Cured	Yes

(*Continued*)

Table 5 (Continued).

Reference	Age/Sex	Diagnosis	Strain	IV/CVI/ IT/IVT Tigecycline	Days to CSF Sterilization	Toxicity	Infection Outcome	Survival
[30]	Neonate/ Male	VP shunt infection	*Klebsiella pneumonia*	IV,1.2 mg/kg/d, q12h IVT, 4 mg/d	24	None	Cured	No (Died of a blood-stream infection)
[31]	33/Male	Intracranial infection	*Acinetobacter baumannii*	IV, 100 mg q12h IVT, 5 mg q12h	7	Hepatic damage (suspected)	Cured	Yes
[32]	56/Male	Ventriculitis	*Acinetobacter baumannii*	IV, 100 mg q12h IVT, 2 mg q12h IVT, 4mg q12h	22	None	Cured	Yes
[33]	68/Male	Pyogenic ventriculitis	*Acinetobacter baumannii*	IV, 50 mg q12h (after a loading dose of 100 mg) CVI, 1 mg q6h IVT, 2 mg q8h	19	None	Cured	Yes
[34]	70/ Female		*Acinetobacter baumannii*	IV, 50 mg q12h (after a loading dose of 100 mg) IVT, 2mg /q12h	17	None	Cured	Yes
[35]	53/Male	Intracranial infection	*Klebsiella pneumoniae*	IVT, 5mg q12h	9	None	Cured	Yes
[36]	31/Male	Intracranial infection	*Acinetobacter baumannii*	IV, 100 mg q12h IT, 5 mg q24h	33	None	Cured	Yes
[37]	16/ Female	Meningitis	*Acinetobacter baumannii*	IV, 50 mg q12h IT, 5mg q24h	51	None	Cured	Yes
[37]	80/Male	Intracranial infection	*Acinetobacter baumannii*	IV, 50 mg q12h IT, 5mg q24h	27	None	Cured	Yes

Abbreviations: NR, not reported; IV, intravenous; IT, intrathecal; IVT, intraventricular; CVI, continuous ventricular irrigation; VRE, vancomycin-resistant enterococcus; VP, ventriculoperitoneal.

The limitations of this study should be mentioned. Firstly, IT or IVT injection of tigecycline is off-label usage. Secondly, only two cases were assessed which were too limited to precisely estimate the effect of tigecycline in the CNS infection. Further prospective and well-designed clinical trials are required, especially with large samples, to further evaluate the therapeutic effects of tigecycline in patients with CRKP infection in the CNS.

Conclusion

It is a huge challenge to cure healthcare-related meningitis and ventriculitis which were caused by CRKP. Timely and effective surgical drainage and anti-infectious treatment are important measures to improve the efficacy and reduce the mortality of these patients. Due to poor prognosis and high mortality in CRKP intracranial infection, as well as too low penetration of commonly used antibiotics into BBB, IT or IVT tigecycline therapy may be an effective choice for the treatment of intracranial infection with CRKP, especially in the nowadays, the resistance rate of superbacteria to antimicrobials remains high.

Ethics Approval and Informed Consent

This study was approved by Ruijin Hospital Institutional Review Board and has been performed in accordance with the ethical standards laid down in "Declaration of Helsinki 1964" and its later amendments or comparable ethical standards. Two patients were enrolled in the study and informed consent forms were signed by the patients.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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