Intrathecal injection of tigecycline in treatment of multidrug-resistant *Acinetobacter baumannii* meningitis: a case report

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ABSTRACT

The ubiquitous *Acinetobacter baumannii* is an important and troublesome pathogen of nosocomial infection. Multidrug-resistant *A. baumannii* meningitis is very difficult to treat, usually with high mortality. The disease is generally associated with craniotomy, but rarely with lumbar puncture. However, in our case, a 45-year-old male construction worker suffered multidrug-resistant *A. baumannii* meningitis associated with lumbar puncture. The patient responded poorly to the initial treatment with an intravenous infusion of tigecycline. However, later treatment with an intrathecal injection of tigecycline (concentration 1 mg/mL) at a dose of 10 mg every 12 hours proved to be highly efficacious. Thus, intrathecal injection of tigecycline should be seriously considered as a treatment for multidrug-resistant *A. baumannii* meningitis.

BACKGROUND

Acinetobacter baumannii is widely found in hospitals. Critically ill patients, old people and patients with weak immunity are susceptible to *A. baumannii* meningitis, which has high mortality. Two studies on *A. baumannii* meningitis in neurosurgical patients have respectively reported a mortality rate of 71.4% and 72.7%.^{1,2} Multidrug-resistant *A. baumannii* ventriculitis has been reported to be associated with external ventricular drainage.^{3,4} Although lumbar puncture as an invasive procedure may also lead to infection, multidrug-resistant *A. baumannii* meningitis associated with lumbar puncture has been rarely reported. Treatment of the disease can be very difficult. It has been shown that intravenous infusion of tigecycline results in low cerebrospinal fluid (CSF) concentrations,^{5,6} and it fails to achieve a clinical response in the treatment of *A. baumannii* cerebritis.⁵

So far no studies on the successful treatment of multidrug-resistant *A. baumannii* meningitis with intrathecal injection of tigecycline have been reported. Therefore this would be the first.

CASE PRESENTATION

The patient presented with disturbance of consciousness on the 51st day after an operation for brain injury. CT imaging showed formation of subdural effusion after craniotomy. A lumbar puncture was carried out to determine CSF pressure, and laboratory analysis of the CSF was performed. The results of the CSF examination are presented in table 1. The CSF leucocyte count was $4 \times 10^6/L$.

On the first day after lumbar puncture, the patient had sudden onset of fever (peak 39.0°C). His temperature increased to 40.0°C on the second day, and therefore lumbar puncture was carried out again. Central nervous system infection was diagnosed from the yellow turbid CSF (figure 1) and an increase in CSF leucocyte count to $1522 \times 10^6/L$.

INVESTIGATIONS

There was no history of adverse drug reactions in the patient and his family.

TREATMENT

Intravenous vancomycin and meropenem were first administered empirically on the diagnosis of meningitis. Two days after the second lumbar puncture, CSF culture showed that multidrug-resistant *A. baumannii* was only sensitive to tigecycline (table 2), so intravenous vancomycin and meropenem were replaced by an intravenous infusion of tigecycline, which was administered at a dose of 50 mg (a dose approved by the Food and Drug Administration (FDA)) every 12 hours after a loading dose of 100 mg. Tigecycline used in each intravenous infusion was dissolved in 100 mL 0.9% NaCl, achieving a concentration of 0.5 mg/mL. Meanwhile, continuous lumbar CSF drainage via a lumbar subarachnoid catheter was performed. After a 1-week course of intravenous tigecycline, high fever persisted and disturbance of consciousness gradually deteriorated. Daily CSF examination results showed that the CSF leucocyte count continued to increase and reached $9714 \times 10^6/L$. Facing the therapeutic challenge posed by *A. baumannii*'s exclusive sensitivity to tigecycline and the poor efficacy of intravenous tigecycline, the chief pharmacist of our hospital recommended that intrathecal injection of tigecycline be seriously considered as a new therapy. After obtaining consent from the patient's next of kin and approval of the ethics committee of Shengli Oilfield Central Hospital in compliance with the Helsinki Declaration, intrathecal injection of tigecycline at a dose of 10 mg every 12 hours was carried out through the lumbar subarachnoid catheter, while intravenous infusion of tigecycline was discontinued. Tigecycline used in each intrathecal injection was dissolved in 10 mL 0.9% NaCl, achieving a concentration of 1 mg/mL. Continuous lumbar CSF drainage was suspended for 2 hours after each intrathecal injection of tigecycline. Six days later, daily CSF examination results showed that the CSF leucocyte count had decreased to a normal level, and the patient's temperature gradually decreased.

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Table 1 Clinical course and cerebrospinal fluid (CSF) examination

Hospital stay	Highest body temperature (°C)	Blood WBC $\times 10^3/\text{mm}^3$	Sample	CSF cells/ mm^3	CSF glucose (mmol/L)	CSF protein (mg/dL)	Antimicrobial therapy
Day 51	36.5	6.1	CSF from lumbar puncture	4	3.80	27.0	None
Day 53	40.0	13.5	CSF from lumbar puncture	1522	1.8	171.8	Vancomycin 1 g q12h meropenem 2 g q8h
Day 55	40.2	15.8	CSF from catheter	5299	0.6	354.2	Intravenous tigecycline 50 mg q12h after a loading dose of 100 mg
Day 58	40.1	20.7	CSF from catheter	7236	0.4	451.3	Intravenous tigecycline 50 mg q12h
Day 60	40.5	22.5	CSF from catheter	8820	0.3	490.5	Intravenous tigecycline 50 mg q12h
Day 61	40.1	26.8	CSF from catheter	9714	0.1	515.0	Intravenous tigecycline 50 mg q12h
Day 62	40.5	27.3	CSF from catheter	9151	0.1	565.1	Intrathecal injection of tigecycline 10 mg q12h
Day 64	39.5	18.9	CSF from catheter	2387	1.6	271.8	Intrathecal injection of tigecycline 10 mg q12h
Day 66	38.5	12.2	CSF from catheter	930	2.1	238.3	Intrathecal injection of tigecycline 10 mg q12h
Day 67	36.9	9.7	CSF from catheter	89	2.8	96.8	Intrathecal injection of tigecycline 10 mg q12h
Day 68	36.5	8.4	CSF from catheter	2	3.4	37.9	None

q12h, every 12 hours; WBC, white blood cell count.

Figure 1 Yellow turbid cerebrospinal fluid because of multidrug-resistant *A baumannii* meningitis.

OUTCOME AND FOLLOW-UP

Eventually the patient's temperature was normal and his CSF was colourless and transparent (figure 2) with a CSF leucocyte count of $2 \times 10^6/\text{L}$. The CSF cultures were negative, so 3 days later the lumbar subarachnoid catheter was removed. The multidrug-resistant *A baumannii* meningitis was cured by

Table 2 Cerebrospinal fluid (CSF) for multidrug-resistant *A baumannii* culture and drug sensitivity test

Antimicrobial drug	Kirby-Bauer antibiotic test (mm)	Minimum inhibitory concentration ($\mu\text{g}/\text{mL}$)	Sensitivity to drug
Ampicillin/sulbactam		≥ 32	Resistant
Ceftazidime		≥ 64	Resistant
Ciprofloxacin		≥ 4	Resistant
Levofloxacin		≥ 8	Resistant
Imipenem		≥ 16	Resistant
Meropenem	6		Resistant
Gentamicin		≥ 16	Resistant
Tobramycin		≥ 16	Resistant
Amikacin		≥ 64	Resistant
Piperacillin/tazobactam		≥ 128	Resistant
Cefepime		≥ 64	Resistant
Ceftriaxone		≥ 64	Resistant
Cotrimoxazole		≥ 320	Resistant
Minocycline	11		Resistant
Cefoperazone/sulbactam	15		Resistant
Tigecycline	17		Susceptible

intrathecal injection of tigecycline. CSF progress during treatment is presented in table 1. No adverse reactions were found during the intrathecal injection of tigecycline or in the following 3 months.

DISCUSSION

Neurosurgical patients with CSF leakage are at high risk of infection by *A baumannii* and developing meningitis.⁷ In our case, the patient developed multidrug-resistant *A baumannii* meningitis related directly to a lumbar puncture.

Because of excessive use of antibiotics, treatment options for multidrug-resistant *A baumannii* are limited.⁸ Intraventricular

Figure 2 Colourless transparent cerebrospinal fluid after intrathecal injection of tigecycline in successful treatment of multidrug-resistant *A baumannii* meningitis.

colistin is a potentially effective treatment for multidrug-resistant *A baumannii* infections of the central nervous system,^{3 9–12} but adverse reactions, including impaired renal function and nervous system damage, have limited its usage. Moreover, production of colistin has been discontinued in China. Therefore colistin was absent in the CSF culture and drug sensitivity of our case. Tigecycline has shown promising in vitro activity on pan-drug-resistant *Acinetobacter*, and some studies have reported its treatment effect on meningitis caused by multidrug-resistant *A baumannii*.^{5 13} Tigecycline specification authorised by the FDA does not include central nervous system infection, but a drug sensitivity test in our case showed that only tigecycline was effective against *A baumannii* meningitis.

Although tigecycline is expensive and not readily available, it should be administered when patients with serious CSF infections are in a life-threatening situation. Intravenous tigecycline for treatment of our patient resulted in poor efficacy despite it being performed in accordance with the instructions, but intrathecal injection enabled tigecycline to fully exert its therapeutic effect, restoring CSF to a completely normal state within 6 days. The treatment outcome suggests that intravenous tigecycline could not reach the minimum inhibitory concentration in the CSF as previously reported.^{5 6}

Intrathecal injection of drugs may cause pain, numbness and dysaesthesias, muscle spasm, weakness, hypertension, tachycardia, hypotension, syncope, transient unilateral ipsilateral facial weakness, major motor seizure, spinal seizure, transient bladder impairment,¹⁴ or even unusual sensorineural hearing loss.¹⁵ It is difficult to evaluate adverse effects from only one case report,

Learning points

- ▶ Intrathecal injection of tigecycline may be worth considering as last-line therapy for the treatment of multidrug-resistant *Acinetobacter baumannii* meningitis.
- ▶ Intrathecal injection of tigecycline changes the evolution of central nervous system infections and accelerates the healing process after infection by multidrug-resistant *A baumannii*.
- ▶ The application, efficacy and safety of tigecycline are worth further evaluation.

but we did not see any. The probability of occurrence of adverse reactions during intrathecal injection of tigecycline is uncertain, so it is necessary to pay attention to this issue in clinical practice.

Correction notice This paper has been amended since it was published Online First. The authors have asked us to point out that they are all from the same institution.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The ethics committee of Shengli Oilfield Central Hospital.

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Patient's perspective

Intrathecal injection of tigecycline was successful in treating our kin who had multidrug-resistant *A baumannii* meningitis. We really appreciate the doctors' efforts and agree to the publication of this report. We hope the practice will be helpful for other patients with multidrug-resistant *A baumannii* meningitis.