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Case Report
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Intrathecal tigecycline is a safe and effective treatment for central nervous system infections

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Both the safety and effectiveness of intrathecal tigecycline (TGC) for treatment of infections of the central nervous system (CNS) are discussed using the clinical findings from a study of a recent patient who came to our attention, along with a literature review. Although penetration into the CNS is low (approximately 11%), intraventricular TGC could help treat patients with severe post- neurosurgical CNS infections. The use of multiple routes of TGC administration appears to be encouraging and should be considered in managing life-threatening intraventricular infections.

Keywords: Tigecycline, Central nervous system bacterial infections, Intrathecal injections, Multi drug resistance

Introduction

Tigecycline (TGC) is a glycylcycline antibiotic widely employed for systemic (intravenous) treatment of skin-skin structures and intraabdominal infections caused by susceptible gram-positive and gram-negative bacteria. Experiences with infections of the central nervous system (CNS) are limited [1], while those encompassing intrathecal administration are even rare. Combined intravenous and intrathecal treatment has been used in a few cases of CNS infections due to multi-resistant, gram-negative pathogens [2–19].

The report was approved by the Institutional Review Board of Azienda Ospedaliera di Cosenza, Cosenza, Italy and written informed consent was obtained from the patient for publication of this case report.

Case Report

After a subarachnoid hemorrhage, a 51-year-old male received external ventricular drainage (EVD) after a ventriculoperitoneal shunt became infected by *Staphylococcus aureus*, leading to a clinical picture of CNS infection (ventriculitis). A baseline computed tomography (CT) scan of his head revealed endovascular treatment of embolization at the apex of the basilar artery using a simple coiling technique, with evidence of metal coils at the level of the interpeduncular cistern, which generated artifacts. The scan also revealed the presence of a cerebral spinal fluid (CSF) shunt catheter with right transfrontal and extreme proximal access in the anterior recesses of the third ventricle, with thickening and inhomogeneity of the frontoparietal subgaleal soft tissues delimiting the shunt catheter, a ventricular system of dimensions within the limits, and midline structures on axis.

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The *S. aureus* strain proved to be resistant to beta-lactams, macrolides, and clindamycin but fully susceptible to glycopeptides and TGC (minimum inhibitory concentration, <0.12 μg/mL).

Together with full-dose intravenous teicoplanin, TGC was administered by both intravenous (full dose) and intraventricular (IVT) routes, the latter at 1 mg twice daily, followed by 5 mg twice daily in a 0.9% saline solution (at a final concentration of 1 mg/mL), maintaining a closed IVT shunt for 2 hours.

Recommended antimicrobial therapy has included the use of 400 mg of teicoplanin in sodium chloride 0.9% intravenous solution 100 mL injection every 12 hours for 3 days, then 400 mg/day plus 100 mg of TGC in sodium chloride 0.9% intravenous solution of 250 mL as a loading dose, followed by 50 mg in sodium chloride 0.9% intravenous solution 100 mL every 12 hours. To enhance antimicrobial activity, use of the IVT route followed a recommended protocol. First, on the second day of therapy, the dose of intravenous TGC was reduced to 49 mg in sodium chloride 0.9% intravenous solution 100 mL every 12 hours, and 1 mg of TGC was administered intraventricularly every 12 hours (slow injection into the lateral ventricles via an EVD was recommended). On the 3rd day of therapy, assuming adequate tolerability, the dose of TGC was reduced to 45 mg in sodium chloride 0.9 intravenous solution 100 mL every 12 hours, administering 5 mg TGC intraventricularly every 12 hours. The overall duration of therapy was 14 days, with microbial sterilization of the CSF and negativity of blood cultures. The TGC used in each intrathecal injection was diluted in 10 mL of 0.9% NaCl, resulting in a concentration of 1 mg/mL. After each IVT injection, the CSF drain was temporarily closed for 2 hours to prevent premature lavage of the drug. Daily chemophysical and microbiological monitoring of the CSF was performed using EVD. Complete blood counts were obtained, and C-reactive protein, procalcitonin, creatinine, creatine phosphokinase, alanine transaminase, lipase, and electrolyte levels were monitored daily. A CT scan of the head on day 14 documented shunt catheter removal along the proximal path in which air was bubbling and hypodensity due to parenchymal pain was highlighted. The ventricular system was slightly reduced in size. Together with full normalization of CSF parameters, these assessments demonstrated both efficacy and safety of TGC administered by an intrathecal route (Table 1). The patient was discharged from the hospital after confirming no residual infection or ventricular enlargement.

The decision to use TGC both intravenously and intrathecally was based on three considerations. First, the intensive care and neurosurgery units of our hospital have a high risk of nosocomial infections due to gram-negative microorganisms, particularly *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Second, because the patient had been recently hospitalized for more than 4 weeks, we assumed he had been colonized by nosocomial organisms. Third, during the first days of treatment with teicoplanin, the patient continued to have a fever.

Discussion

While combined intravenous and intrathecal antibiotics have been used successfully to treat multidrug-resistant (MDR) CNS infections, most of these were nosocomial in origin, and intrathecal TGC has been used in only a few cases of spinal arachnoiditis or intracranial infections caused by MDR *A. baumannii* strains [2–19]. The present report is the first to apply TGC to patients with gram-positive CNS infections. TGC is a new, intravenous, broad-spectrum antibiotic that is a derivative of minocycline and a member of the glycylcyclines. It is part of a new class of semisynthetic antibacterial agents developed to treat polymicrobial infections caused by MDR to gram-positive and gram-negative pathogens, overcoming the main tetracycline-resistance genetic mechanisms associated with efflux pumps and ribosomal protection proteins that decrease the activity of other tetracyclines.

Table 1 Laboratory and cerebrospinal fluid characteristics

Characteristic	Baseline	Day 14
Laboratory characteristic		
White blood cell ($\times 10^6$/mL)	18.9	10
Neutrophils ($\times 10^6$/mL)	14.8	5.7
Percentage	78.4	57.9
Lymphocytes	2.1	2.7
Percentage	11.2	27.1
Monocytes ($\times 10^6$/mL)	1.8	1.2
Percentage	9.7	12.1
C-reactive protein (mg/L)	301.7	62.9
Fibrinogen (mg/dL)	763	337
Cerebrospinal fluid test		
Appearance	Colorless, hazy	Colorless, clear
Karyocyte cell	33	9
Red blood cell	0	0
Mononuclear cell (%)	25	40
Multinucleated cell (%)	75	60
Immunoglobulin G (mg/dL)	16.8	4.99
Albumin (mg/dL)	84.9	37.4
Glucose (mg/dL)	64	54.9
Gram stain	Occasional gram-positive cocci	No organisms seen
Culture	*Staphylococcus aureus*	No growth

Table 2 Characteristics of adults previously reported with CNS infection treated with intraventricular TGS (2020–2022)

Patient No.	Study	Year	Age (yr)/ sex	Country	Underlying disease (s)	Primary infection	Organ-ism(s)	TGC MIC (mg/L)	TGC concen-trations (mg/L)	Side effects	TGC, IV/ CVI/IVT	LOT (days)	Co-adminis-tered antibiotics	Outcome	Time to CSF sterilization (day)
1	Lauretti et al. [2]	2017	22/M	Italy	A giant pituitary adenoma, post-resection CSF leak	Post-neurosurgical meningitis	XDRAB	2 μg/mL	NR	Chemical ventriculitis, myelitis (CST)	IV, 100 mg/ q12 hr; IVT, 2 mg/(q24–12 hr)	IVT, 45; 1 month from the restart of the IVT IV, 14; IVT, 14	CST IVT, 120,000/ q12 hr; MEP IV, 2 g/q8 hr; VAN IV, 1 g/ q12 hr	Improved	75
2	Fang et al. [3]	2017	50/M	China	Craniocerebral injury	Post-neurosurgical meningitis	XDRAB	2 μg/mL	NR	None	IV, 100 mg/ q12 hr; IVT, 3–4 mg/q12 hr	IV, 14; ITV, 14	CES IV, 3 g/ q12 hr	Improved	14
3	Wang et al. [4]	2017	45/M	China		Post-lumbar punc-ture meningitis	MDRAB	NR (Kirby-Bauer antibiotic test, 17 mm)	1 mg/mL	None	IV, 50 mg q12 hr; IVT, 10 mg q12 hr	IV, 7 (discon-tinued before starting IVT TGC); IVT, 6	None	Improved	6
4	Long et al. [5]	2018	55/M	India	Intracerebellar hemorrhage, CSF leak, hydrocephalus, EVD	Post-neurosurgical ventriculitis	MDRAB	16 μg/mL	NR	None	IV, 100 mg q12; IVT, 4 mg/day	IV, 14; CVI, 14; IVT, 3	CES IV, 2 g/ q8 hr	Improved	12
5	Tsolaki et al. [6]	2018	55/F	Greece	Aneurysmal subarachnoid hemorrhage	Post-neurosurgical VM	MDRAB	2 μg/mL	NR	None	IV, 100 mg q12 yr; IVT, 4 mg/day	IV TGC, 14; IVT TGC, 15; IVT CST, 22	IVT CST, 250 × 10^3 IU qd	Improved	4
6	Tsolaki et al. [6]	2018	50/M	Greece	Intraventricular mass resection, cerebral edema, EVD	Post-neurosurgical VM	MDRAB	1 μg/mL	NR	None	IV, NR; IVT	IV TGC, 15; IVT TGC, 15; IVT CST, 30	CST, 250 × 10^3 IU qd	Improved	5
7	Tsolaki et al. [6]	2018	48/M	Greece	Cerebellum spontaneous hemorrhage, EVD	Post-neurosurgical VM	MDRKP	NR	NR	None	IV, NR; IVT	IV TGC, 9; IVT TGC, 9; IVT CST, 11	CST, 125 × 10^3 IU qd	Improved	3
8	Liu et al. [7]	2018	70/F	China	Sub-arachnoid hemorrhage	Post-neurosurgical ventriculitis	XDRAB	≤1 μg/mL	NR	None	IV, 50 mg q12 hr; IVT, 2 mg q12 yr	IV TGC, 16; IVT TGC, 10	CES IV, 3 g/ q8 hr	Improved	10
9	Wu et al. [8]	2018	67/M	China	Cerebral hemorrhage, EVD	Post-neurosurgical meningitis	MDRKP	NR	The trough concentrations of TGC in CSF for the three different dosages of TGC IV-ICV combined administration were 0.313, 1.290, and 2.886 mg/L for 40 mg IV/10 mg ICV, 45 mg IV/5 mg ICV, and 50 mg IV/1 mg ICV TGC, respectively	None	IV, 45 mg q12 hr, 40 mg q12 hr; IVT, 1 mg q12 hr, 5 mg q12 hr, 10 mg q12 hr	NR	TMP/SMX 480 mg q12 hr per os	Improved	42

(Continued to the next page)

Table 2 Continued

Patient No.	Study	Year	Age (yr)/ sex	Country	Underlying disease (s)	Primary infection	Organ-ism(s)	TGC MIC (mg/L)	TGC concen-trations (mg/L)	Side effects	TGC, IV/ CVI/IVT	LOT (days)	Co-adminis-tered antibiotics	Outcome	Time to CSF sterilization (day)
10	Curebal et al. [9]	2018	28 days/ M	Turkey	Congenital hydrocephalus, VPS placement	VPS infection	MDRAB After three negative CSF the patient was dis-charged	1 μg/mL	NR	None	IV, 1.2 mg/ kg/day; IVT, 4 mg/day	IV TGC, 24; IVT TGC, 14	MEP IV, 120 mg/kg/day for 34 days IVT AMK, 30 mg/ day for 10 days discontinued before starting IVT TGC	Died after the 1st month of discharge, because of pneumonia and sepsis. Blood culture was positive for XDRAB sensitive for colistin. TGC MIC value was 16 μg/ mL	7
11	Pratheep et al. [10]	2019	Baby born at 27 wk gestation	India	Baby was born to a mother with prelabor premature rupture of membranes. At birth, baby had respiratory distress	Ventriculitis	XDRAB	NR	NR	None	IVT, 3 mg/day	IVT TGC, 2 wk	IVT CST, 5 mg/day for 4 wk	Improved	14
12	Deng et al. [11]	2019	17/M	China	Tuberculous meningitis	Post-neurosurgery intracranial infection	XDRAB	1 μg/mL	NR	None	IV,47.5 mg q12 hr; IVT, 4 mg q12 hr (after 4 days the clinical pharmacist advised changing from IVT to TGC ITC infusions; 4 mg daily)	IV TGC, 39; IVT TGC, 39	IV FOS, 4 g q8 hr; IV CES, 3 g q8 hr; after 4 days changed to IV MEP 2 g every q8 hr	Improved	39
13	Soto-Hernán-dez et al. [12]	2019	38/M	México	Recent review of VPS. Hydrocephalus after cryptococcal meningitis in HIV+	Post-neurosurgical ventriculitis	MDRKO	< 2 μg/mL	Peak concentra-tions achieved at 2 hr after the dose of be-tween 178 and 310 μg/mL	None	IVT, 5 mg q24 hr	IVT TGC, 11	MEP, 6 g qd; AMK 15 mg/ kg/day	Improved	3
14	Zhong et al. [13]	2020	33/M	China	Severe craniocerebral trauma	Post-neurosurgical intracranial infection	XDRAB	2 μg/mL	NR	Hepatic toxici-ty, no neuro-toxic side ef-fects	IV, 100 mg/ q12 hr; IVT, 5 mg/q12 hr During the 7 days of the use IV/IVT TGC, CSF cellular and biochemical CSF markers improved; however, XDRAB was still present.	IV TGC, 100 mg q12 hr for 7; IVT TGC, 5 mg q12 hr for 7	Sequential use of POLB IV, 100 mg q12 hr IV, POLB IVT, 10 mg qd, changed to qod × 2 wk IVT 4 days later	Improved	7 (after starting IV/ IVT POLB)

(Continued to the next page)

Table 2 Continued

Patient No.	Study	Year	Age (yr)/ sex	Country	Underlying disease (s)	Primary infection	Organ-ism(s)	TGC MIC (mg/L)	TGC concen-trations (mg/L)	Side effects	TGC, IV/ CVI/IVT	LOT (days)	Co-adminis-tered antibiotics	Outcome	Time to CSF sterilization (day)
15	Abdallah et al. [14]	2020	53/M	Saudi Arabia	Cerebral hemorrhage in DM and uncontrolled hypertension	Post-neurosurgical meningitis and ventriculitis	MDRAB	4 μg/mL (intermediate susceptibility)	NR	After 8 hr of administering the first dose of IVT TGC, the patient developed myoclonic seizures for 4 min	IVT, TGC 2 mg q12 hr	IV TGC, 22; IVT TGC, 14; IV MEP, 24; IV TMP-SMX, 19	High-dose tigecycline (200-mg IV stat dose followed by 100-mg IV q12 hr), TMP/ SMX (1,920-mg IV q6 hr)	Improved	14 (after starting IVT TGC)
16	Li et al. [15]	2021	68/M	China	Decompressive craniectomy and evacuation of traumatic cerebellar hematoma	Post-neurosurgical ventriculitis	MDRAB	NR	NR	None	IV, 50 mg q12 hr +; CVI, 4 mg q24 hr (in 50 mL of NS, at a rate of 12.5 mL/hr at a frequency of q6 hr) After 3 days: IV, 50 mg q12 day + IVT, 2 mg in 4 mL of NS in 2 min at a frequency of q8 hr	IV TGC + CVI, 3; IV TGC + IVT, 7		Improved	10 (after starting IV + CVI), 7 (after starting IV + IVT)
17	Huang et al. [16]	2022	16/F	China	Craniotomy for resection of vestibular schwannomas	Post-neurosurgery meningitis	XDRAB	2 μg/mL	NR	None	IV, 50 mg q12 hr; IVT, 5 mg q24 days	IV TGC + IVT TGC, 4 wk	IV CES, 3 g q8 days for 4 wk	Improved	4 wk
18	Huang et al. [16]	2022	80/M	China	Craniotomy for removal of frontal meningiomas	Post-neurosurgical ventriculitis	XDRAB	2 μg/mL	NR	None	IV, 50 mg q12 hr; IVT, 5 mg q24 days	IV TGC + IVT TGC, 10	IV CES, 3 g q8 days for 10 days	Improved	10
19	Li et al. [17]	2022	57/M	China	Hematoma removal after craniocerebral injury	Post-neurosurgical ventriculitis	CRKP	2 μg/mL	NR	None	IV, 100 mg qd; IVT, 3 mg q12 hr	14	IVT AMK, 0.8 g IV + 30 mg IVT qd	Improved	14
20	Wang et al. [18]	2022	53/M	China	Suboccipital decompression for an acute cerebellar infarction	Post-neurosurgical ventriculitis	CRKP	0.5 μg/mL	NR	None	IVT, 5 mg q12 days	IVT TGC, 6 (after intrace-rebroventricu-lar injection of POLIB)	IV CAZ/AVI, 2.5 g + MAP, 2 g q 8 dahs	Improved	6 (22nd day of hospital-ization)
21	Li et al. [19]	2022	31/M	China	Ventricular drainage performed subarachnoid hemorrhage	Post-neurosurgical ventriculitis	XDRAB	≤2 μg/mL	NR	None	IV, 100 mg q12 hr combined with IVT 5 mg qd	IVT TGC + IVT TGC, 33	IV MEP, 2 g IV q8 hr; VAN, 1 g q12 hr; IVT POLB, 50,000 IU qd	Improved	33 (after IV + IVT TGC), 29 (after IVT POLB)

CNS, central nervous system; TGC, tygecicline; MIC, minimum inhibitory concentration; IV, intravenous; CVI, continuous ventricular irrigation; IVT, intraventricular therapy; LOT, length of treatment; CSF, cerebrospinal fluid; M, male; F, female; XDRAB, extensive drug resistant *Acinetobacter baumannii*; NR, not reported; CST, chemical sterilization therapy; MEP, meropenem; VAN, vancomycin; CES, cefoperazone-sulbactam; MDRAB, multidrug-resistant *Acinetobacter baumannii*; EVD, external ventricular device; MDRKP, multidrug resistant *Klebsiella pneumoniae*; TMP/SMX, trimethoprim-sulfamethoxazole; VPS, ventriculo-peritoneal shunt; AMK, amikacyn; ITC, intrathecal; FOS, fosfomycin; POLB, polimixyn B; DM, diabetes mellitus; POLIB, polimyxin B; CAZ/AVI, ceftazidime/avibactam.

TGC is structurally similar to tetracyclines but is a chemically modified monocycline with addition of a t-butylglycylamido side chain to the C9 carbon of the "D" tetracycline ring, resulting in expansion of the TGC spectrum of antibacterial activity against a wide spectrum of gram-positive and gram-negative pathogens.

As a bacteriostatic inhibitor of bacterial protein translation via reversible binding to a helical region on the 30S subunit of bacterial ribosomes, TGC prevents the incorporation of amino acid residues into elongated peptide chains, inhibiting peptide formation and bacterial growth.

TGC is the first glycylcycline antibacterial drug that inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking the entry of aminoacyl transfer RNA molecules into the A site of the ribosome.

Both the dose and administration schedules of intrathecal TGC remain to be defined, but when a CNS infection is of concern, intravenous administration must be ruled out because of poor drug penetration of the blood-brain barrier. IVT administration of TGC is emerging as an effective therapeutic option for the treatment of CNS infections, particularly those caused by MDR organisms for which there are few other therapeutic opportunities.

Although the descriptions are limited, a narrative review of a letter summarized in Table 2 [2-19] highlights many relevant articles published, attesting to the strength of interest in this topic. Considering the potential neutral but irreversible effects correlated with high concentrations of TGC, further studies are needed to verify the safest and most effective dosages. IVT therapy remains an off-label therapeutic possibility and, pending further precision therapy studies, should be reserved as an individualized therapy resource for the treatment of severe infections, possibly under therapeutic drug monitoring guidance. The dose of TGC used by Soto-Hernández et al. [12] produced levels 15 to 20 times the minimum inhibitory concentration of the bacteria for up to six hours with adequate tolerance. Doses smaller than 5 mg and those administered more than twice daily have been recommended as the safest and most effective regimen [16]. Moreover, further research is necessary to determine the role of TGC in the treatment of CNS infection. The safety of IVT injections of this drug, as well as the pharmacokinetics and pharmacodynamics in this patient setting, should be analyzed in larger studies involving patients with postsurgical and serious infections by gram-positive organisms.

We recently published a brief report, the first of its kind, documenting the safety and efficacy of high-dose TGC as a salvage therapy in five Italian patients with serious CNS rickettsiosis [1]. Despite the low concentrations of TGC in the CSF compared with the minimum inhibitory concentration, some reports describe a positive evolution of the therapy for CNS infections by MDR organisms with TGC [1]. A drug may accumulate in polymorphonuclear cells and then be delivered to the site of infection in higher-than-anticipated concentrations or lead to minor subinhibitory effects. Although penetration into the CNS is minimal (approximately 11%), TGC delivered by IVT may be able to treat patients with severe post-neurosurgical CNS infections [1]. The decision to use TGC both intravenously and intrathecally in our patient was based on three considerations. First, the intensive care unit and neurosurgery units of our hospital both have a high risk of nosocomial infections due to gram-negative microorganisms, particularly *E. coli*, *K. pneumoniae*, and *A. baumannii*. Second, the patient had been recently hospitalized for more than 4 weeks and was assumed to be colonized by nosocomial organisms. Third. during the first days of treatment with teicoplanin, the patient continued to run a fever.

The use of multi-route TGC appears to be effective and should be considered for managing life-threatening IVT infections.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization, Investigation: Mastroianni A; Data curation: Greco S, Mauro MV; Formal analysis: all authors; Writing–original draft: all authors; Writing–review and editing: all authors.

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