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Case report

A case report of treatment of a streptococcal brain abscess with ceftobiprole supported by the measurement of drug levels in the cerebrospinal fluid

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ABSTRACT

In this paper, we describe the case of a patient admitted to our hospital because of a brain abscess due to *Streptococcus intermedius*. The management of brain abscess is challenging given the limited potential drug options with effective penetration into both the central nervous system and the abscess capsule to achieve adequate therapeutic concentrations. Due to the high anti-streptococcal activity of ceftobiprole and the availability of ceftobiprole therapeutic drug monitoring in our hospital, we decided to treat the patient with ceftobiprole. To maximize the antimicrobial effect of ceftobiprole, we chose a prolonged intravenous infusion, and we monitored its concentrations in both plasma and cerebrospinal fluid.

1. Introduction

Streptococcus anginosus group, formerly called "*Streptococcus milleri* group", includes three distinct species: *S. anginosus, Streptococcus constellatus* and *Streptococcus intermedius* [1]. Virtually all strains (93%) of *S. intermedius* are non-hemolytic (alpha- or gamma-hemolysis), while 38% of *S. constellatus* and 12% of *S. anginosus* are β-hemolytic [2]. They are found in normal flora of the oral cavity, paranasal sinuses, upper airways, gastrointestinal tract, and female urogenital tract. Even though these organisms are part of the commensal flora, they can also act as opportunistic pathogens and are remarkably known for their ability to cause brain abscesses due to contiguous spread from parameningeal foci [3,4] or through overt or subclinical hematogenous dissemination with relative sparing of endocardium [5]. It is noteworthy that differences in virulence factors between members of the *S. anginosus* group might be partly responsible for the impressive competence of *S. intermedius* in causing brain abscess compared to *S. anginosus* and *S. constellatus*

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[2,5]. Treatment of brain abscess due to *S. intermedius* with penicillin associated with an aminoglycoside has been suggested as effective treatment by some authors [5]. Due to poor antibiotic penetration into brain lesions through the blood–brain barrier (BBB), neurosurgical intervention should be considered for abscess size >2.5 cm in diameter [4]. Ceftobiprole is a parenteral cephalosporin showing high antimicrobial activity against streptococci [6]. As such the drug might show promise for implementation in streptococcal brain abscess treatment regimens. In this paper, we describe the case of a patient admitted to our hospital because of a brain abscess due to *S. intermedius*. Considering the challenging management of brain abscesses, the limited selection of antibiotic choices that can effectively penetrate both the central nervous system (CNS) and the abscess capsule to achieve efficacious therapeutic drug concentrations and given the availability of ceftobiprole therapeutic drug monitoring (TDM) in our hospital, we consistently administered ceftobiprole. To maximize the antimicrobial effect of ceftobiprole, we chose a prolonged intravenous infusion, and we monitored its concentrations in both plasma and cerebrospinal fluid (CSF).

2. Case report

A 50-year-old man with a history of cocaine and opioid use disorder in treatment with methadone was admitted to our hospital because of acute onset of change of mental status, fever, headache, and malaise. The blood pressure was 130/70 mmHg, the pulse rate 60 beats per minute and the oxygen saturation 96% while he was breathing room air. Physical examination revealed poor dentition, right upper quadrant tenderness and hepatosplenomegaly. Hematologic and serum chemical laboratory data showed a white blood cell (WBC) count of 8940/μl (differential count: 86% neutrophils, 7% lymphocytes, 0.3% eosinophils), normocytic and normochromic anemia (hemoglobin of 11.6 g/dL), platelet count of 250,000/μL, C-reactive protein (CRP) of 45 mg/l (reference range 0–5 mg/L), fibrinogen of 625 mg/dL. Computed tomography (CT) scan of the brain showed seven infratentorial and supratentorial rounded ring-enhancing lesions with central low attenuation consistent with brain abscesses. A magnetic resonance imaging (MRI) showed multiple hyperintense ring enhancing lesions with perilesional edema (Fig. 1). Blood cultures and lumbar puncture (LP) were performed and empirical anti-infective therapy with trimethoprim-sulfamethoxazole and meropenem was started. Intravenous (IV) dexamethasone

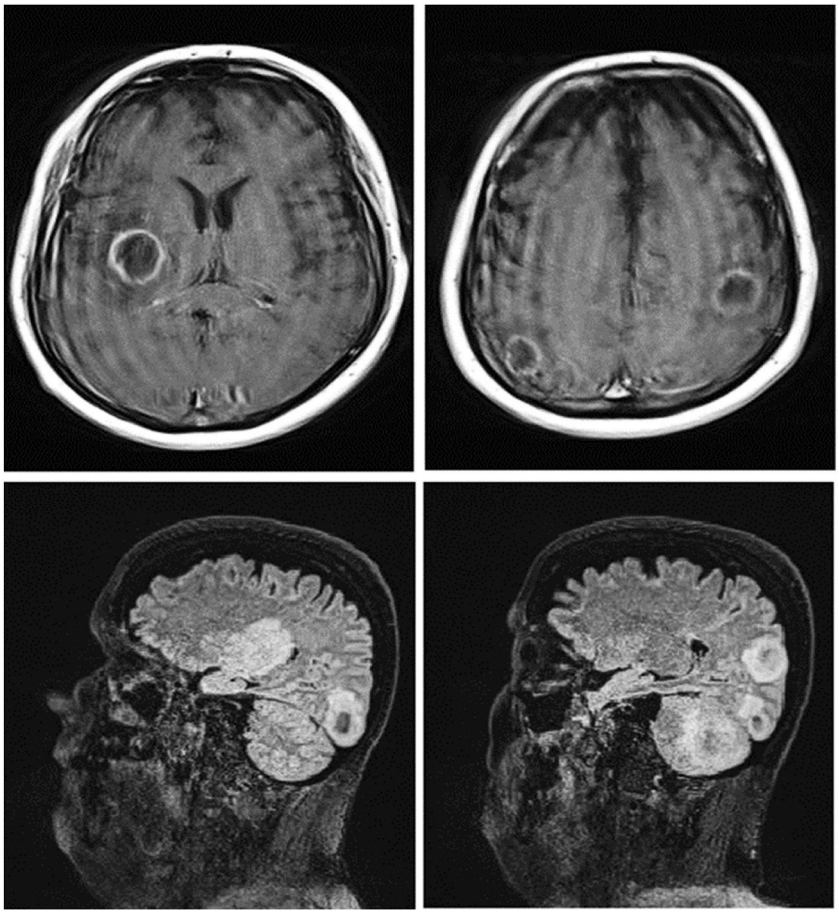

Fig. 1. MRI showing multiple intracranial expansive formations with grossly round shape, consisting of a central portion and rim enhancing with contrast medium. All lesions appear surrounded by edema. Larger lesions are located in: a,b) bilaterally in the temporal and parietal lobes; c,d) the occipital region and left cerebellar hemisphere (resulting in mass effect on the fourth ventricle).

was also started. Cerebrospinal fluid analysis showed elevated protein concentration (1154 mg/l) with elevated CSF WBC count (111/μL, differential count: 5% polymorphonuclear leukocytes, 60% lymphocytes, 35% monocytes) with reduced glucose ratio (glucose 57 mg/dl, RATIO 0.43) and normal lactate level. Polymerase chain reaction (PCR) multiplex meningitis panel (Biofire® FilmArray ME Panel, BioMérieux, Marcy-Etoile, France), CSF *Toxoplasma* DNA PCR, CSF Gram stain, standard culture methods for CSF microorganisms and blood cultures turned out to be negative. Human Immunodeficiency Virus (HIV) serological tests proved to be negative. No heart valve vegetations were seen on transthoracic (TTE) and transesophageal echocardiogram (TEE). Since an orthopantomogram showed residual roots, dental caries and a periapical granuloma, tooth extraction, scaling and root planing were performed. After three weeks of antibiotic therapy, the patient underwent stereotactic aspiration of the largest lesion; additional CSF samples for microbiological examinations were collected during the procedure. The Biofire® FilmArray BCID2 (BioMérieux, Marcy-Etoile, France), a comprehensive panel consisting of a total of 43 targets, including resistance mechanisms [7] was employed on the CSF samples. Since the BCID2 is only approved for use on positive blood cultures, we opted for spiking 300 μl of CSF in a blood culture bottle (BACT/ALERT® FAN® PLUS BioMérieux Italia S.p.A.). The suspension was incubated for 2 hours. Subsequently, 300 μl of cultured CSF and media were collected from the bottle and processed according to the manufacturer's instructions. Once correct loading and rehydration were verified, the run was initiated. Results were automatically displayed in a report and showed positivity for *Streptococcus* spp. Results of 16S ribosomal RNA gene sequencing were also positive for *S. intermedius*. Cultures of aspirated specimens documented the growth of *S. intermedius* as well. Antimicrobial susceptibility testing (AST) is reported in Table 1. Based on microbiological results, the initial empirical antimicrobial treatment regimen was shifted to ceftobiprole 500 mg 8-hourly 3-h infusion time and IV fosfomycin 24 g/day continuous infusion. In order to individualize anti-infective therapy according to a PK/PD-guided approach, the plasmatic TDM of ceftobiprole was coupled with the determination of ceftobiprole in CSF. A high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection method was used to quantify ceftobiprole in plasma and CSF. One milliliter of plasma or 0.5 mL of sample was spiked with cefepime as an internal standard (IS) and then subjected to solid-phase extraction (SPE) before HPLC analysis. A reverse phase chromatography separation was performed using Shimadzu Nexera-i equipped with UV detector (Shimadzu, Kyoto, Japan) and with an InfinityLab Poroshell 120 EC -C18 column (3.0 × 50 mm with 2.7- μm particle size) (Agilent, Santa Clara, United States). The mobile phase, consisting of a mixture of acetonitrile and 30 mM phosphate buffer (pH 3.15), was used in a gradient mode and detection was performed at a wavelength of 296 nm. The method was linear in the concentration range of 1.0–30.0 microg/mL in both plasma and CSF. Because of the 8- hourly intermittent 3-h duration intravenous infusion of ceftobiprole, we performed three venous blood samples to characterize the PK profile of ceftobiprole: before dosing, at the end of the drug infusion, and 4 h after dosing. TDM of plasmatic ceftobiprole was performed 5 days after the start of antibiotic infusion, when steady state was durably reached, because virtually no relevant clinical conditions occurred affecting the half-life of the drug. Total ceftobiprole serum concentrations were measured at a 6-day interval. We performed TDM in CSF collected after two weeks of targeted antimicrobial therapy by means of LP performed immediately before the scheduled ceftobiprole dose. The free plasmatic concentrations of ceftobiprole as estimated according to drug protein binding are reported in Table 2. Analysis of CSF collected after two weeks of ceftobiprole and fosfomycin combination therapy showed a protein concentration of 808 mg/l with virtually normal WBC count (5/μL), normal glucose and lactate levels. Measured CSF ceftobiprole concentration was 1.2 mg/l. The corresponding mean interdose total plasma concentration of ceftobiprole was 9.74 mg/L (SD ± 4.46). This resulted in an estimated ceftobiprole CSF/plasma ratio of 12%. Following a three-week course of intravenous therapy with noticeable amelioration of clinical condition and radiological findings, the treatment was transitioned to oral tedizolid, and the patient was subsequently discharged. Two months later, brain imaging showed further improvement and the patient achieved complete neurological recovery The patient completed antibiotic therapy 156 days after diagnostic brain biopsy was performed.

2.1. Patient perspective

From the patient perspective the treatment did not impact negatively on his quality of life. Moreover, he did not experience any adverse event.

Table 1
Antibiotic susceptibility testing of Streptococcus intermedius and MIC interpretation according to European Committee on Antmicrobial Susceptibility Testing (EUCAST) Breakpoint tables for interpretation of MICs, Version 13.0, valid from 2023 to 01-01.

Antibiotic	MIC (mg/l)	Interpretation
Amoxicillin	0.094	S
Benzylpenicillin	0.023	S
Cefotaxime	0.064	S
Ceftaroline	0.012	
Ceftobiprole	0.094	
Ceftriaxone	0.064	S
Clindamycin	256	R
Vancomycin	1	S
Gentamicin	4	
Daptomycin	≤0.25	
Tedizolid	≤0.25	S
Trimethoprim-sulfamethoxazole	0.25–4.75	

Table 2
Total plasmatic concentrations of ceftobiprole were measured at different time points both at the first performance of therapeutic drug monitoring (TDM) and six days later (second TDM). Free plasmatic concentrations are estimated from ceftobiprole protein binding.

	Total ceftobiprole pre-dosing plasmatic concentrations (mg/L)	Total ceftobiprole 3 hours post-dosing plasmatic concentrations (mg/L)	Total ceftobiprole 4 hours post-dosing plasmatic concentrations (mg/L)	Estimated free ceftobiprole pre-dosing plasmatic concentrations (mg/L)	Estimated free ceftobiprole 3 hours post-dosing plasmatic concentrations (mg/L)	Estimated free ceftobiprole 4 hours post-dosing plasmatic concentrations (mg/L)
First TDM (March 24, 2022)	4.98	15.94	8.11	4.18	13.39	6.8
Second TDM (March 30, 2022)	5.00	10.39	13.84	4.2	8.73	11.63

3. Discussion

We decided to treat our patient with ceftobiprole given TDM availability in our hospital and because of its potent activity against streptococci. This remarkable anti-streptococcal activity might be due to heightened and broader affinity to penicillin-binding proteins (PBPs) such as PBP2x compared to other cephalosporins, surpassing that of penicillin and ceftriaxone [8]. Despite several studies demonstrating the broad antibacterial activity of ceftobiprole in a variety of experimental models and in humans, little is known about its potential in the treatment of CNS infections. In a study involving rabbits, the penetration of ceftobiprole through inflamed and non-inflamed meninges reached about 16% and about 2% of serum levels, respectively [9]; the penetration of ceftobiprole in cerebrospinal fluid was even slightly higher than cefepime, which was used as a comparator [9]. Due to its physico-chemical properties, mainly represented by hydrophilicity, medium molecular weight, and ionic polarity, ceftobiprole is unable to freely reach CSF and brain tissue by passive diffusion. Indeed, ceftobiprole is a weak substrate of several transport proteins, such as organic cation transporters (OCTs) or P-glycoprotein, which are localized in the epithelial cells of both the BBB and the choroid plexus in the blood-cerebrospinal fluid barrier (BCSFB) [10]. These conditions cause a low penetration rate in CSF, similar to other cephalosporins compounds, ranging from 0.7 to around 2.3% in uninflamed meninges and increasing up to 16% in case of meningitis [9,11]. To shed light on this clinical and pharmacological issue, we explored the concentration of ceftobiprole in CSF since, to the best of our knowledge, no data on its CNS penetration are available, especially in the setting of little or no meningeal inflammation. We administered the standard ceftobiprole dose of 500 mg every 8 hours. To take advantage of the time-dependent properties of ceftobiprole antimicrobial effect, we prolonged the infusion time (3 hours instead of 2 hours). Two weeks after initiation of antimicrobial therapy, we performed both plasmatic and CSF TDM when steady state was reached. Because no renal alterations occurred in our patient, no relevant changes in the pharmacokinetics of ceftobiprole were expected. We believe that the ceftobiprole concentration we found in CSF reflects the achievement of the aggressive PK/PD target of 70–100 % T > MIC [12] in CSF due to several pharmacological preconditions: 1) the ceftobiprole plasmatic levels show a low intra- and interpatient variability in case of multiple-dose administration, causing low fluctuations of the steady-state drug plasma concentrations, not influenced by sex, body weight or ethnicity [13,14]. 2) ceftobiprole PK is time-independent and is characterized by slight, not clinically relevant, drug accumulation occurring after multiple drug administration [15]; 3) generally, in case of multiple drug administrations, the drug fluctuation and the peak-to-trough ratio are reduced when the absorption of the compound in the target tissue is slowed down as in case of the selective transport of ceftobiprole mediated by OCTs across the BBB and the BCSFB; 4) BBB and BCSFB permeability is not altered in uninflamed meninges, whereas meningitis induces physio-pathological conditions weakening the selectivity of the aforementioned barriers. In the rabbit meningitis model mentioned above [9], Stucki et al. demonstrated that ceftobiprole more extensively penetrates into CSF in case of meningitis than in case of no inflammation, and that the CSF concentration decreases more slowly in non-inflamed meninges compared to inflamed ones, maintaining stable concentration until the consecutive administration [9]; 5) probably, the cephalosporin concentrations in brain tissues are higher than that estimated by CSF, since some studies demonstrated a CSF to blood penicillin concentration ratio higher in ventricles than CSF concentration measured by traditional lumbar puncture [16,17]. Because our patient showed a negligible grade of meningeal inflammation, the ceftobiprole concentration measured in the CSF perhaps represented the mean stable drug exposure between doses in the CNS because of the anatomic and physiologic characteristics of the BBB, BCSFB and CSF, as previously stated. Consequently, we can assume that drug exposure in the CNS was approximately tenfold above the ceftobiprole MIC of *S. intermedius* and persisted for the entire dosing interval (T > MIC of 100%). Moreover, because of the likely lower variability of ceftobiprole concentrations in CSF compared with plasmatic concentrations, we estimated the ceftobiprole CSF/plasmatic ratio to be 12% by comparing the concentrations in CSF with the mean of the three plasmatic samples. Considering that the pharmacodynamic parameter for the bactericidal activity of β-lactams is to reach concentrations at least four times higher than the MIC [18–20], we attained an excellent result in our patient. Furthermore, patient did not show any adverse effects that are associated with ceftobiprole such as gastro-intestinal disorders, urticaria, dysgeusia, seizures, infusion site reaction. This case report shows some limitations due to the nature of the study, with limited possibility of generalizing the validity of the results and the inability to establish a clear cause-effect relationship. Moreover, significant biases might arise concerning the retrospective study design and the focus on an uncommon case, for which we have employed a newer therapeutic option other than standard antimicrobial treatments, such as penicillin or third generation cephalosporines [21].

4. Conclusion

Our experience brings innovative data the field of CNS infection treatment, showing that ceftobiprole has a good penetration into CSF even in a human being; furthermore, the use of ceftobiprole allowed avoiding aminoglycosides or glycopeptides, whose side effects (e.g., ototoxicity, nephrotoxicity) are relatively frequent. In particular, in our patient we measured ceftobiprole penetration in the CSF through little or no inflamed meninges: antibiotic therapy was started one month before LP, along with corticosteroids for anti-inflammatory purposes, and CSF characteristics showed normal levels of glucose cells and lactate. This work also emphasizes the importance of TDM in clinical practice in order to optimize antibiotic therapy in difficult-to-treat life-threatening infections such as CNS infections.

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Ethics declaration

Ethic approval was not required. For this case report, the patient provided written informed consent for the publication of the anonymized case details and images.

Consent for publication

Written informed consent was acquired from the patient who consented to publish all images, clinical data, and other data included in the manuscript.

Data availability

Data of the present manuscript have not been deposited into a publicly available repository. Data will be available from the corresponding author on request.

CRediT authorship contribution statement

Simone Giuliano: Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Jacopo Angelini:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sarah Flammini:** Writing – original draft. **Paola Della Siega:** Data curation. **Eleonora Vania:** Writing – original draft, Data curation. **Luca Montanari:** Writing – original draft. **Denise D'Elia:** Data curation. **Jessica Biasizzo:** Formal analysis. **Alberto Pagotto:** Data curation. **Carlo Tascini:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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