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TITLE PAGE - Brief Report

Title:
CSF concentration of cefotaxime in adult patients with pneumococcal meningitis: a multicentre retrospective study

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Running title

Cefotaxime in adult pneumococcal meningitis CSF

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Abstract

***Background and objectives**:* Pneumococcal meningitis is a devastating disease that requires adequate meningeal antibiotic penetration to limit the mortality. Despite a large usage in this indication, data about CSF concentration of cefotaxime during pneumococcal meningitis in adults are scarce. Therefore we aimed to describe the CSF concentration obtained after high-dose cefotaxime administration in adult patients treated for *Streptococcus pneumoniae* meningitis.

***Patients and methods**:* In this multicentre, observational, retrospective study, cases of adult patients with *S. pneumoniae* meningitis hospitalized between January 2013 and October 2019 for whom cefotaxime concentration was measured in CSF were reviewed.

***Results**:* Cefotaxime concentration was analysed in 44 CSF samples collected among 31 patients... Median (IQR) age was 61 years (52;69). Dexamethasone was administered in 27 subjects. Median (IQR) cefotaxime daily dosage was 15 g (12;19) corresponding to 200 mg/kg (150;280). CSF samples were collected 5 days after cefotaxime initiation roughly. Median (IQR, range) cefotaxime CSF concentration was 10.3 mg/L (4.8;19.3, 1.2-43.4). Median (range) MIC of *Streptococcus pneumoniae* was 0.25 mg/L (0.008-1) (n=22). The median (IQR, range) CSF/MIC ratio was 38 (12;146, 4-1844). Twenty-five CSF concentrations (81 %) were above 10 times the MIC. Cefotaxime was discontinued in 2 patients for toxicity. In-hospital mortality rate was 29%.

***Conclusions**:* Adult patients with pneumococcal meningitis treated with high dose of cefotaxime (200 mg/kg/day) had elevated CSF concentrations with satisfying pharmacokinetics/pharmacodynamics parameters and tolerability profile. This study brings reassuring pharmacological data regarding the use of high dose cefotaxime monotherapy for treating pneumococcal meningitis with susceptible strains to cefotaxime.

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TEXT (1217 words)

Introduction

Streptococcus pneumoniae meningitis is a devastating disease with the highest morbidity and mortality among community-acquired bacterial meningitis. [1] Cefotaxime is a third-generation cephalosporin (3GC) widely recommended for the treatment of pneumococcal meningitis. French guidelines for management of acute bacterial meningitis recommend dosage of cefotaxime to be weight-based without any upper limit whereas international guidelines recommend a maximum daily dosage of 12 g. [2–4] The adequacy between antibiotic penetration in CSF and antibiotic susceptibility of *Streptococcus pneumoniae* is a cornerstone to achieve satisfying pharmacokinetics/pharmacodynamics (PK-PD) targets in this lethal disease. The increasing incidence of *Streptococcus pneumoniae* isolates with reduced susceptibility to 3GC is therefore a matter of concern. [5] Given these epidemiological changes, data about cefotaxime penetration in CSF might offer relevant information. [6] However, very limited data exist about CSF penetration of cefotaxime when meningeal dose are used in adults treated for pneumococcal meningitis. We aimed to describe the CSF penetration of cefotaxime in adult patients treated for *S. pneumoniae* meningitis.

Patients and methods

We conducted a multicentre, observational, retrospective study. Adult patients hospitalized between January 2013 and October 2019 for whom cefotaxime concentration was measured in CSF as part of the routine care were identified in the participating centres and among the participants of the COMBAT cohort (NCT02916732). Among them, individuals treated for proven pneumococcal meningitis, with either positive CSF culture or CSF PCR assay for *Streptococcus pneumoniae,* were included. Medical charts were retrospectively reviewed to collect clinical, pharmacological and microbiological data. CSF parameters were reported at the time of cefotaxime concentration measurements in CSF. Concomitant cefotaxime plasma concentrations (same day) were collected when available. All CSF concentrations were measured within 48h following CSF sampling and were systematically stored at -80°C if they were

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not immediately performed. Antibiotic concentrations were measured in CSF and plasma using a liquid-chromatography coupled with mass-spectrometry or diode-array detector validated assay. Limit of quantitation was 1 mg/L. A steady-state plasma concentration was defined by a cefotaxime concentration measured at least 24 hours after treatment initiation. Plasma concentrations were considered as trough levels when continuous infusion was used or when discontinued infusion was used and plasma samples collected just before infusion.

Cefotaxime MIC were determined using an Etest strips or Vitek 2 automated system (bioMérieux, France) depending on usual practices of the different centres and according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The study received ethical approval from the Research Ethics Committee on Infectious and Tropical Diseases (CERMIT2019-0706, IRB00011642). Participants were informed of the study in accordance with French legal standards.

A Wilcoxon rank sum test was used to compare the cefotaxime CSF levels between patients with and without dexamethasone with a significance level of 0.05.

Results

Study population

In total, 31 individuals were included. Their characteristics are reported in **Table 1**. Median (IQR) age was 61 years (52;69). Dexamethasone was administered in 27 subjects (87 %). Median (IQR) cefotaxime daily dosage was 15 g (12;19) corresponding to 200 mg/kg (150;280). Sixteen out of 28 patients received cefotaxime by continuous intravenous infusion (3 missing data).

Pharmacokinetics-pharmacodynamics analysis

Forty-four CSF concentrations (from 1 to 4 per patient) and 28 plasma concentrations (from 0 to 4 per patient) were measured. The median (IQR) time between cefotaxime initiation and CSF sampling was 121 hours (78-194), all above 24 hours (2 missing data). For patients who did not receive continuous infusion, the median (IQR) time between cefotaxime preceding infusion and CSF sampling was 3.3 (1.5-

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5.3) hours. Median (IQR, range) CSF concentration was 10.3 mg/L (4.8;19.3, 1.2-43.4) (see **Table 1**). Median (IQR) plasma concentration was 60.5 mg/L (31.3-81.7). Plasma concentrations were trough levels in 75% (21/28) of patients. For paired CSF and plasma cefotaxime measurements (n=28 paired samples), the median (IQR) calculated CSF/plasma ratio was 21.6 % (8.6-28.5). The cefotaxime MIC of *S. pneumoniae* was reported for 22 (71%) subjects. Median (IQR, range) MIC was 0.25 mg/L (0.036;0.5, 0.008-1). Based on the cefotaxime MIC of each patient's pneumococcal strain the median (IQR, range) CSF/MIC ratio was 38 (12-146, 4-1844) (n=31 CSF samples). Twenty-five CSF concentrations (81 %) were above 10 times the corresponding MIC. CSF cefotaxime levels did not differ between dexamethasone- and non-dexamethasone-treated patients (p=0.59). Considering the weight-based daily dosage and the associated CSF concentration, 6 patients received less than 150 mg/kg/day (n=9 samples), 6 between 150 and 199 mg/kg/day (n=8 samples), 11 between 200 and 280 mg/kg/day (n=13 samples), 6 above 280 mg/kg/day (n=10) with a median (IQR) CSF concentration of 7.5 mg/L (1.2;29.3), 10.3 mg/L (2.2;15.4), 5.4 mg/L (1.6;23.8), and 18.3 mg/L (3.0;43.4) respectively (see **Table 2**).

Clinical outcomes

Cefotaxime was discontinued because of toxicity in 2 patients (8.0 %, 6 missing data). One with acute kidney injury experienced a neurological degradation with electroencephalogram abnormalities while having elevated cefotaxime concentrations in CSF (19.3 mg/L) and plasma (254.9 mg/L). The details on toxicity were not available for the other patient. In hospital mortality rate was 29 % (9/31).

Discussion

Previous studies assessing CSF penetration of cefotaxime were mostly done in children and revealed lower concentrations than in this study, [7] or variable concentrations similarly to those observed here. [8] Interestingly, a previous PK/PD modelling study suggested that cefotaxime dosages of 4g/6h would be sufficient to achieve CSF levels above the MIC for 90% of time, even for pneumococcal strains with an MIC of 2, which appear close to the results observed in the current study. [9]

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The IDSA and the ESCMID guidelines for acute bacterial meningitis treatment in adults recommend a cefotaxime daily dosage from 8 to 12 g, in association with vancomycin or rifampicin when reduced susceptibility to penicillin is suspected, which is the case in France. [3,4] Meanwhile, French guidelines promote a monotherapy of cefotaxime with a dose-weighted adjustment without any upper limit dosage and recommend dosages based on cefotaxime susceptibility which range from 200 mg/kg when MIC is below 0.5 mg/L (susceptible strain) to 300 mg/kg when MIC is between 0.5 mg/L and 2 mg/L (intermediate strain) or unknown. [2]

Recently, Mizrahi and coll. reported a case of therapeutic failure in a patient with 3GC-intermediate *Streptococcus pneumoniae* meningitis. [10] After several days of ceftriaxone monotherapy the patient' state worsened and repeated CSF culture revealed a 3GC-resistant *Streptococcus pneumoniae* isolate. This resistance emergence possibly occurred due to insufficient exposition of antibiotics. [11] Because a limited exposition to antibiotics can lead to resistant strain selection, it appears necessary to target CSF concentrations far above the MIC although the optimal CSF/MIC ratio target remains uncertain. [12]

In France, the incidence of pneumococcal meningitis with decreased 3GC susceptibility reached its lowest point in 2014 when 1.5% of strains were cefotaxime-intermediate and none resistant. Since then, this proportion increased relatively with 6.6% in 2017 with rare resistant strains (0.7%). [13] The pharmacological results of our study suggest that using high-dose cefotaxime (200 mg/kg) seems a reasonable option to treat cefotaxime-susceptible strains. Notably, the highest CSF concentrations observed in this cohort were found in patients receiving daily dosage above 280 mg/kg with a median of 18 mg/L and were higher than previous reports in adults receiving meningeal dose of cefotaxime. [14,15] Those very high dosages corresponded approximately to the initial empirical dosage proposed by French guidelines and could be sufficient to treat even cefotaxime-intermediate strains.

The global satisfying tolerability of cefotaxime despite the high doses used in the study population is in accordance with previous reports of very high doses of other 3GC in patients treated for suspected CNS infections. [16]

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The limitations of our study include: i) the retrospective design, ii) a small sample size, which prevents to analyse the factors associated with CSF cefotaxime penetration and patients' outcomes, iii) some missing data regarding the indication of CSF antibiotic dosing and the dosage of dexamethasone (although it is likely that the recommended dosage of 10 mg/q6h was administered), iv) a possible selection bias because repeated CSF analysis is not systematically recommended but only in case of elevated MIC or unfavourable outcome. [2]

High dose cefotaxime regimens (200 mg/kg) used in adults during pneumococcal meningitis lead to elevated CSF levels associated with satisfying PK-PD parameters in CSF. Despite its limitations this study brings reassuring pharmacological and clinical data regarding the use of high dose cefotaxime as recommended in France for treating pneumococcal meningitis with 3GC susceptible strains.

Authors' contributions

Paul Le Turnier (Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Methodology, Writing – original draft), Najoua El Helali (Investigation, Writing – review and editing), Romain Guilhaumou (investigation), Benoit Pilmis (Investigation, Writing – review and editing), Lionel Jean Velly (Investigation) Matthieu Revest (Investigation), Anne Gaelle Leroy (Methodology, Writing – original draft), Xavier Duval (Conceptualization, Investigation, Writing – review and editing), Florian Lemaitre (Investigation, Writing – review and editing), Matthieu Grégoire (Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft).

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Transparency declarations

None to declare

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TABLES

Table 1: **Description of study population's characteristics and outcomes, antibiotic therapy characteristics, CSF parameters and pharmacological results (n=31 patients)**

Study population characteristics	
Age, years, median (IQR)	61 (52;69)
Weight, Kg, median (IQR)[a]	75.5 (60.7;90.2)
Glomerular filtration (CKD-EPI) at each CSF samples, mL/min/1.73 m^2, median (IQR)[b]	91 (78;105.3)
Dexamethasone, n (%)	27 (87)
In-hospital mortality, n (%)	9 (29)
S. pneumoniae MIC, mg/L, median (min;Q1;Q3;max)[c]	0.25 (0.008;0.032;0.5;1)
Characteristics of the cefotaxime therapy	
Daily dosage, g, median (IQR)[d]	15 (12;19)
Daily dosage, mg/Kg, median (IQR)[e]	200 (150;280)
Continuous infusion, n (%)[f]	16 (57)
Frequency in intermittent infusion, n/24h, median (IQR)	6 (4;6)
Discontinuation for toxicity, n (%)[g]	2 (8)
CSF parameters in samples used for pharmacological measurements	
CSF samples with antibiotic dosing, n	44

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CSF sampling via LP, n (%)	33 (75)
White blood cells/mm^3, median (IQR)[h]	111 (32;565)
Protein g/L, median (IQR)[i]	2.2 (1.2;2.7)
Glucose mmol/L, median (IQR)[j]	3.28 (1.65;6.11)
Pharmacological results of cefotaxime measurements	
CSF concentration, mg/L, median (min;Q1;Q3;max)	
- All patients (n=44)	10.5 (1.2;4.9;19.3;43.4)
- Patients with dexamethasone (n= 33)	9.3 (1.6;4.5;15.4;39.1)
- Patients without dexamethasone (n=11)	12.3 (1.2;6.5;20.4;43.4)
Plasma concentration, mg/L, median (min;Q1;Q3;max)[k]	60.5 (13.5;31;81.7;254.9)
CSF/Plasma concentration ratio, %, median (min;Q1;Q3;max)[k]	21.6 (1.4;8.6;28.5;183.8)
CSF/MIC ratio, median (min;Q1;Q3;max)[l]	38 (4;12;146;1844)
CSF/MIC > 10, n (%)[l]	25 (81)

CTX, Cefotaxime; CKD-EPI, Chronic Kidney Disease EPIdemiology collaboration, LP, Lumbar puncture; PK-PD, Pharmacokinetics-pharmacodynamics; min, minimum; Q1, first quartile; Q3, third quartile; max, maximum.

[a]missing data: n=3/31; [b]creatinin clearance values were collected for each CSF sample, missing data: n=4/44; [c]missing data: n=9/31; [d] missing data: n=1/44; [e] missing data: n=4/44; [f] missing data: n=3/31; [g]missing data: n=6/31; [h]missing data: n=11/44; [i]missing data: n=12/44; [j]missing data: n=13/44; [k]missing data: n=17/44; [l]missing data: n=14/44.

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Table 2. CSF concentrations of cefotaxime according to weight-based daily dosage (n=40 dosages, 4 missing data)

Daily dosage (mg/kg/day)	<150	[150-199]	[200-280]	>280
Number of patients	6	6	11	6
Number of dosages	9	8	13	10
Time since CTX initiation, hours, median	120	144	96	193
Creatinin clearance, ml/min, median	51	77.5	86.0	96.5
Creatinin clearance < 30ml/min, n	4 (1 md)	0	1 (2 md)	0
CSF concentration, mg/L, median (range)	7.5 (1.2;29.3)	10.3 (2.2;15.4)	5.4 (1.6;23.8)	18.3 (3.0;43.4)

Md, missing data; CTX, Cefotaxime

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