

Original Article

PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support



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ARTICLE INFO

Article history:
Available online 1 March 2019

Keywords:
ECMO
Antibiotic plasma concentrations
Therapeutic drug monitoring

ABSTRACT

Introduction: Optimisation of antibiotic therapy for extracorporeal membrane oxygenation (ECMO) patients remains a pharmacological challenge. The objective of this study was to observe the plasma concentrations of commonly used antibiotics in intensive care for patients treated with extracorporeal membrane oxygenation.

Patients and methods: The PHARMECMO study was a pilot, prospective study, conducted in a cardiac surgery intensive care unit. Every adult patient under ECMO support, with known or suspected sepsis and receiving antibiotic therapy, was eligible for inclusion. Plasma concentrations of antibiotics were determined by a combination of liquid chromatography and mass spectrometry.

Results: Forty-four eligible patients were enrolled for 68 inclusions on a twelve-month period. For the association piperacillin-tazobactam (n=19), 68.7% of CT50 and 93.7% of Cmin reached the pharmacokinetic goals defined (64 mg.L⁻¹ for CT50 and 16 mg.L⁻¹ for Cmin). For cefotaxime (n=12), the pharmacokinetic goals (4 mg.L⁻¹ for CT50 and 1 mg.L⁻¹ for Cmin) were achieved in 100% of the cases for CT50 and in 81.8% of the cases for Cmin. Regarding imipenem (n=10), the pharmacokinetic goals were 16 mg.L⁻¹ for CT50 and 4 mg.L⁻¹ for Cmin. Only one CT50 was above 16 mg.L⁻¹. For Cmin, 60% of the doses did not reach the target concentration. In our 10 patients, only one patient was considered as reaching the pharmacokinetic goals. Finally, for amikacin (n=6), four Cmax (66.7%) were infra-therapeutics for a target between 60 and 80 mg.L⁻¹.

Conclusion: These preliminary results suggest that therapeutic drug monitoring could optimise the achievement of pharmacokinetic objectives associated with an effective antibiotic therapy. For most patients, the recommended doses of imipenem and amikacin did not achieve the pK targets

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Introduction

ECMO (Extracorporeal Membrane Oxygenation) is a life-support technique used to treat patients with cardiorespiratory failure refractory to conventional therapies. Major advances in

device technology and the publication of the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial [1] or the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial [2] have led to a significant expansion of ECMO use worldwide. Survival for adults supported with ECMO showed continuous improvement over time, with survival rates reported in The Extracorporeal Life Support Organisation's (ELSO) registry [3] of 50% in patients with

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veno-arterial ECMO and up to 70% in patients with veno-venous ECMO. However, more than 60% of adult patients receiving ECMO will develop nosocomial infections, which are associated with longer durations of mechanical ventilation, ECMO support, and hospital stays [4]. Hence, optimisation of antibiotic therapy for ECMO patients remains a pharmacological challenge. Increase in the volume of distribution (Vd), altered clearance or drug extraction by the circuit could induce significant changes in antibiotics pharmacokinetics under ECMO assistance, as shown in paediatric populations [5]. However, recent studies in an adult population did not confirm these previous results [6–10].

The objective of this prospective pilot study was to observe the plasma concentrations of commonly used antibiotics (β -lactams, glycopeptides, fluoroquinolones and aminoglycosides) in intensive care for adult patients treated with extracorporeal membrane oxygenation.

Patients and methods

Design

The PHARMECMO study was a pilot prospective observational study, conducted in an eighteen-bed adult cardiac surgery intensive care unit at La Pitié-Salpêtrière University Hospital, Paris, France. Adult patients admitted in the ICU for veno-venous (VV ECMO) or veno-arterial ECMO (VA ECMO) assistance with known or suspected sepsis and receiving antibiotic therapy were included. Exclusion criteria were known allergy to studied antibiotics, pregnancy, patients with burns or cystic fibrosis, therapeutic plasma exchanges in the preceding 24 hours. All patients or relatives provided written informed consent to participate.

Data

The following data were collected for all patients: age, gender, weight and body mass index, admission date and ICU admission diagnosis, date of intubation and extubation and the mortality date. With the therapeutic drug monitoring (TDM), the following data were also collected: weight, temperature, heart rate, mean arterial pressure, respiratory rate, inspiratory oxygen fraction, the following biological factors: partial pressure of arterial oxygen (PaO₂), pH, potassium and sodium levels, lactic acid, leukocytes, haematocrit, serum proteins, renal function parameters: serum creatinine, urine output, creatinuria (creatinine clearance was calculated from the 24-h urine using the formula: $CLCr_{ml/min} = [(urine\ Cr, mg/dL) \times (urine\ output, mL)] / [(serum\ Cr, mg/dL) \times (time\ of\ urine\ collection, min)]$), presence of continuous renal replacement therapy (cRRT) (initiation time of cRRT, dialysate and ultrafiltrate rate), data concerning antibiotic therapy, type of drugs, initiation time, posology, type of infusion (continuous, extended or bolus infusion), infusion time, number of doses received before TDM, exact time of the last infusion, data related to ECMO: indication, initiation time, type of ECMO, cannulation site, ECMO course before TDM, ECMO parameters the day of the TDM, data related to the sepsis: pathogens and infection type.

Extracorporeal life support circuit and management

All ECMO equipment was implanted surgically with peripheral or central heparin-coating cannulation. The ECMO circuits used were comprised of a centrifugal blood pump (ROTAFLOW, Centrifugal Pump, Maquet), an oxygenator and cannulas (Edward Lifesciences, Irvine, CA). In case of peripheral VA cannulation, an

anterograde catheter was placed to avoid limb ischaemia. A heat exchanger was also used to maintain normothermia. Crystalloids and/or colloids were used for the priming volume. ECMO parameters were adjusted by the physician to ensure blood oxygen level, the CO₂ removal and an appropriate blood flow. All patients received ECMO circuits anticoagulation with heparin.

Antibiotic treatment, measurements and pharmacokinetic (PK) analysis

The decision to initiate antibiotic therapy was made by the physician taking care of the patient according to clinical, biological and microbiological findings. For β -lactams infused in an intermittent or extended way, two successive TDM were performed respectively at 50% (C_{T50}) at 100% (C_{min}) of the dose interval. For glycopeptides and β -lactams infused in a continuous way, only one TDM was performed to measure the steady state concentration. To be sure to perform therapeutic drug monitoring in a steady state phase, samples were collected after at least 48 hours from the start of antibiotic therapy, at 8:00 a.m. For aminoglycosides and fluoroquinolones, the maximum concentration (C_{max}) was measured 30 minutes after the end of a 30 minutes infusion time. Blood samples were directly sent to the emergency chemistry laboratory to be centrifuged and kept at $-80^{\circ}C$. Those samples were then sent to the microbiological laboratory of Saint-Joseph Hospital. Plasma concentration of the antibiotics was determined using a high-performance liquid chromatography connected to mass-spectrometry.

The pharmacokinetic (pK) objectives chosen for β -lactams were: an antibiotic plasma concentration above 4 times the minimum inhibitory concentration (MIC) during 50% of the dose [6,7,11] and an antibiotic plasma concentration above the MIC during 100% [12] of the dose interval. The target MIC was defined by the clinical breakpoints for *Pseudomonas aeruginosa* defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Vancomycin steady state plasma concentrations were considered adequate if between 20 mg.L⁻¹ and 30 mg.L⁻¹ [13]. Concerning aminoglycoside, C_{max} were considered adequate between 60 mg.L⁻¹ and 80 mg.L⁻¹ [14,15] for amikacin and between 30 mg.L⁻¹ and 40 mg.L⁻¹ for gentamicin and tobramycin. Regarding fluoroquinolones, a C_{max}/CMI > 8 [16] was considered adequate.

Chromatographic analysis was performed with a TLX-1 chromatographic system with two UltiMate 3000 LC pumps. The extraction was performed in Focus Technical mode with an online turbulent flow SPE TurboFlow® MCX-2 column (60 μ m, 0.5 \times 50 mm, Thermo Scientific). Analytical separation was carried out at room temperature in gradient mode with 0.1% of formic acid (v/v) in water (A) or 0.1% of formic acid (v/v) in acetonitrile (B), on a Hypersil® GoldAq column (5 μ m, 50 \times 3mm, Thermo Scientific). The detection was performed with a High Resolution Mass Spectrometric (HRMS) analyser (Exactive Plus, Thermo Scientific) equipped with a heated electrospray ionization source (h-ESI-II). Amikacin analysis was performed with an immuno-turbidimetric method on Indiko Plus analyser (Thermo Fisher) with absorbance determination. The entire methodology was validated following the validation guidelines of the European Medicines Agency (EMA).

Statistical analysis

Discrete variables were expressed as counts (%) and continuous variables as median and interquartile range. The data distribution of TDM was depicted with the use of boxplots (R Software, version 3.3). The comparison between the categorical variables was assessed using Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant.

Ethical considerations

The study was approved by an independent National Research Ethics Committee (Comité de Protection des Personnes Ile de France VI, N°2014-A00043-44), registered in EudraCT (2011-003292-10) and clinicaltrials.gov (NCT03131063).

Results

Forty-four patients were prospectively included on a twelve-month period (May 2014–April 2015), which allowed 68 inclusions. Patient characteristics are shown in Table 1. Some of the patients had been included several times for different antibiotic therapies. Inclusions were made with a minimum interval of 48 hours in case of antibiotics of the same class. All the patients who had been included required mechanical ventilation and the use of a support by catecholamines. The median length of ICU stay was 25 days [17–39]. Among the 68 inclusions, 34 (50%) died during ICU hospitalisation. Patients and ECMO characteristics are shown in Table 1.

Bacteriological data

More than half of the infections were ventilator-associated pneumonias, followed by bacteraemia and operating site infections (Table 2). Almost a quarter of suspected infections were not documented. *Pseudomonas aeruginosa* was the most frequent isolated microorganism (29.4%) (Table 3).

Pharmacological analysis

A total of 115 measures of plasma concentration were made using high-pressure liquid chromatography and mass spectrometry. Among the 68 inclusions, 53 (77.9%) concerned β -lactams. The main studied β -lactams were piperacillin ($n = 19$), cefotaxime ($n = 12$) and imipenem ($n = 10$).

Table 1
Demographic and clinical characteristics of patients.

Patient characteristic	n (%) or median [IQR]
Age (years)	62.5 [58–67]
Female	10 (14.7)
BMI	25.2 [23.4–28.2]
IGS 2	52 [43–67]
Time from ECMO to inclusion	6 [4–14.7]
Duration of ECMO	20 [12–25]
Mortality	34 (50)
Serum proteins (g/L)	48 [44–52]
Plasma creatinine concentration ($\mu\text{mol/L}$)	78 [60–133]
Creatinine clearance (mL/min)	20 [0–69]
CRRT	28 (41)
Indication for ECMO	
Post cardiectomy	19 (27.90)
Dilated cardiomyopathy	17 (25.0)
infective endocarditis	10 (14.7)
Acute myocardial infarction	8 (11.7)
Heart transplantation	6 (8.8)
Other	8 (11.7)
Type of ECMO	
VV	2 (2.9)
VA Peripheral	50 (73.5)
VA central	4 (5.8)
RA - PA	12 (17.6)

BMI: body mass index; IGS 2: index de gravité simplifié 2; COPD: chronic obstructive pulmonary disease; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; VA: veno-arterial; VV: veno-venous; RA-PA: right atrium – Pulmonary artery. The biochemical indices were measured on day of pharmacokinetic sampling.

Table 2
Infected sites.

Infected Sites	n (%)
VAP	35 (51.5%)
Bloodstream infections	6 (8.9%)
Infective endocarditis	4 (5.8%)
Catheter infection	4 (8.8%)
Mediastinitis and local infection of the cannulation site	6 (8.9%)
Urinary tract infection	3 (4.4%)
Not documented	16 (23.5%)

VAP: Ventilator-associated pneumonia.

Table 3
Bacteriological data.

Pathogens	n (%)
<i>Pseudomonas aeruginosa</i>	20 (29.4%)
<i>Klebsiella pneumoniae</i>	13 (19.1%)
<i>E. Coli</i>	11 (16.2%)
<i>Enterobacter cloacae</i>	5 (7.3%)
<i>Morganella morganii</i>	2 (2.9%)
<i>Citrobacter koseri</i>	1 (1.5%)
Other gram negative bacteria	2 (2.9%)
<i>Streptococcus</i>	5 (7.3%)
<i>Staphylococcus epidermidis</i>	4 (5.9%)
<i>Staphylococcus aureus</i>	1 (1.5%)
<i>Enterococcus</i>	1 (1.5%)
<i>Stenotrophomonas maltophilia</i>	1 (1.5%)
<i>Listeria monocytogene</i>	1 (1.5%)

β -lactams

Cefotaxime was dosed in 12 cases. C_{T50} and C_{min} median were respectively 64.7 mg.L^{-1} [20.2–97.5] and 28.6 mg.L^{-1} [7.3–42.1] for a median dose of 7 grams per day [6–8]. Considering a target MIC of 1 mg.L^{-1} , corresponding to the MIC of the enterobacterias to cefotaxime, the pharmacokinetic goals (4 mg.L^{-1} for C_{T50} and 1 mg.L^{-1} for C_{min}) were achieved in 100% of the cases for C_{T50} and in 81.8% of the cases for C_{min} .

Piperacillin was the most represented molecule in our study, with a total of 19 inclusions. The median dose was 4 grams four times a day given using an extended infusion. C_{T50} and C_{min} median were respectively 87 mg.L^{-1} [52.8–155.1] and 61.2 mg.L^{-1} [35.4–109.6]. Taking into account the MIC of the *Pseudomonas aeruginosa* to the piperacillin, the pharmacokinetic goals were 64 mg.L^{-1} for C_{T50} and 16 mg.L^{-1} for C_{min} . Thus, 68.7% of C_{T50} and 93.7% of C_{min} reached the pharmacokinetic goals defined.

Ten patients treated with the association imipenem/cilastatin were included in our study. The median dose of imipenem was 1 gram three times a day. C_{T50} and C_{min} median plasma concentration were respectively 7.3 mg.L^{-1} [4.0–14.6] and 3.3 mg.L^{-1} [1.8–5.4]. Based on the MIC of *Pseudomonas aeruginosa* to imipenem according to the EUCAST (4 mg.L^{-1}), the pharmacokinetic goals were 16 mg.L^{-1} for the C_{T50} and 4 mg.L^{-1} for the C_{min} . Only one C_{T50} was above 16 mg.L^{-1} . For the C_{min} , 60% of the doses did not reached the target concentration of one time the MIC. In our 10 patients cohort, only one patient was considered as reaching the pharmacokinetic goals. Considering a median dose of 1 gram three times a day, 90% of the pair of doses performed were considered as subtherapeutic.

Twelve cases dealing with other β -lactams were included. The results of the pharmacological therapeutic follow-ups are summarised in Table 4. Fig. 1 represents plasma concentrations for cefotaxime, piperacillin and imipenem.

Table 4
Therapeutic drug monitoring.

	n	Dosing regimen (g.d ⁻¹)	MIC	Proportions of adequates
Amoxicillin	6	6	8	66.6
Piperacillin	19	16	16	80.5
Cefotaxime	12	7	1	91.3
Ceftazidime	3	6	8	100
Cefepime	1	6	8	100
Meropenem	2	3–6	2	100
Imipenem	10	3	4	25
Vancomycin	5	2	4	80
Ciprofloxacin	2	0.8	0.5	50

Aminoglycosides

In our study, 8 patients were treated with aminoglycosides. One was treated with gentamycin, another with tobramycin and six with amikacin. The gentamycin peak reached 38.2 mg.L⁻¹ for a dose of 11.1 mg.kg⁻¹. This peak was considered as being in the therapeutic range of 30 and 40 mg.L⁻¹. The tobramycin peak reached 13.7 mg.L⁻¹ with a dosage of 7.1 mg.kg⁻¹, which is below the target concentration. Regarding amikacin, six plasmatic peaks were measured. Four doses (66.7%) were infra-therapeutics by taking a therapeutic zone ranging between 60 and 80 mg.L⁻¹.

Discussion

The β-lactams, which are the most frequently used antibiotics in the ICU, were the main category studied in this work. The three main β-lactams studied showed very different results in terms of achievement of the pK objectives. In the case of cefotaxime, the achievement of the objectives was mostly fulfilled. For piperacillin, the pK objectives also seemed mostly achieved. The concentrations were kept in 88.2% (15/17) of the cases above the *Pseudomonas aeruginosa* MIC. On the other hand, for imipenem, with a dosage of three grams per day, the pharmacokinetic goals were reached only in 10% of the cases. Regarding the aminoglycosides, 62.5% of the peak concentration were sub-therapeutic.

The results of this preliminary study could constitute a first observation of the pK of antibiotics in an adult population under circulatory assistance by VA ECMO in a context of postoperative cardiac surgery. As far as we know, there are no data in this context. *Ex vivo* studies has shown that the use of ECMO could alter drug pharmacokinetics. Drugs sequestration result of the absorption of drugs on the PVC tubing and/or the membrane oxygenator [17]. Lipophilicity and protein binding are the main determinants of circuit adsorption [18–21]. Increased volume of distribution and decreased clearance are also involved in pK alteration during ECMO. Indeed, the different studies available were conducted on

heterogeneous groups of patients, made of medical and surgical patients or patients under VV and VA ECMO in variable proportion. The Ashman and al. study [22] conducted on children or newborns showed that usual doses of cefotaxime enabled sufficient plasma concentrations for an effective treatment. Our results seem to confirm the conclusions of this study in the adult population. Other teams draw different results than ours for piperacillin. In a study published by Donadello and al. [6], the goal of keeping a concentration of piperacillin between 4 and 8 times the MIC during 50% of the time of the inter-doses interval was completed in less than 50% of cases. These results are contradictory with the ones found in our study. Several reasons can explain the difference. First, the population they studied was different, an exclusive respiratory assistance by VV ECMO was used in 65% of the cases, and the prevalence of the renal dysfunction was below than the one in our study. Unlike our study, the doses of piperacillin were adjusted to the renal function. Finally, pharmacological measurements were not always conducted in a steady state plasma concentration, which made the interpretation of their results more delicate considering the frequency of under-dosing during the initial phase of antibiotic therapy. There are no data in regard of the pK of the imipenem under ECMO except for two cases reports [23]. Couffignal and al. [24] noticed that an administration every 6 hours in ICU patients without ECMO was better able to reach the objectives than an administration three times a day. However, even at the highest studied dosages (1 g/6 h), fT > MIC of 100% was reached in only 45% of the cases. These results confirmed our observations and implied the necessity to increase doses. The two studies focusing on the pK of meropenem in patients under ECMO seems to indicate that a dose of 1 g/8 h would maintain a sufficient plasma concentration. In these studies, neither the ECMO, neither extra-renal dialysis seemed to significantly influence pharmacokinetic of meropenem. Likewise, for the amikacin, the study of Gélisse and al. [8] showed that ECMO did not influence the pK of the amikacin, with, however, non-strictly identical groups. In this study, we could notice insufficient peak concentrations in more than 25% of the cases with a dose of 25 mg/kg. Finally, like in all the studies, which had been made on the pK of the antibiotics under ECMO, a wild inter-individual variability was observed. This concept is a major argument for the use of a pharmacological therapeutic management.

Nowadays, there are no formal recommendations regarding the pK objectives to obtain an optimum efficiency. If animal studies define as necessary a fT > MIC between 40% and 70%, several studies suggested that an exposure to higher doses would be necessary. Roberts and al. [25] recently demonstrated that fT > MIC of 100% of the inter-doses interval was necessary. This important concept supported our choices of the pK objectives we wanted to achieve. Indeed, our initial hypothesis was that a probability antibiotic therapy should cater to the most adverse situations involving microorganisms with the higher MIC to antibiotics given.

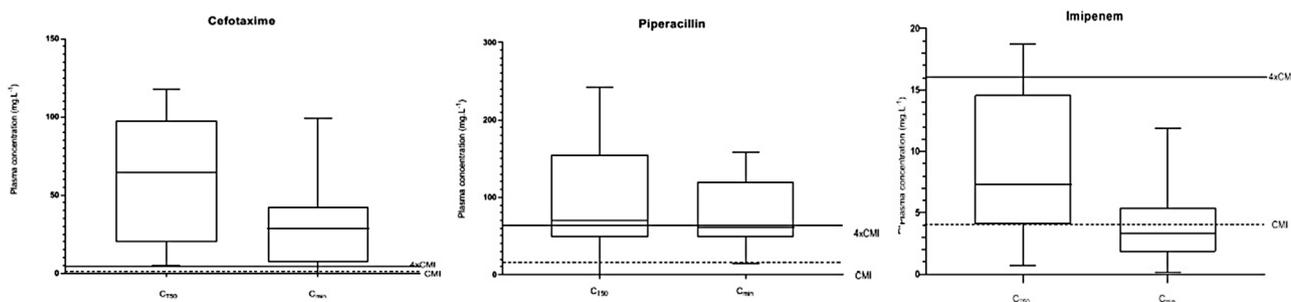


Fig. 1. Plasma concentration at 50% (CT50) and 100% (Cmin) of the dosing interval. Dotted line indicates MIC and the solid line indicates the objective of 4×MIC.

Our preliminary study shows several limits. First of all, it could not conclude on the specific role of the ECMO in terms of impact on the pK of the different antibiotics studied given the lack of control groups. However, the main objective was to assess in which measures antibiotic therapy in patients under ECMO achieves the pK objectives. Our initial hypothesis was that an optimisation of the antibiotic therapy was possible using a pharmacological and therapeutic monitoring in this population with a severe pathology. This work was carried out in the cardiac surgery ICU treating patients with long term circulatory support and heart transplant. The studied population was made of surgical patients in need of a circulatory support by peripheral or central VA ECMO, sometimes associated with another circulatory device. Complications associated with a support by ECMO were different depending on the type of assistance; this could constitute a limit to the external validity of our results. Finally, for some of the antibiotics under study, the low number of patients was a limit for the interpretation of the results.

Conclusion

These preliminary results suggest that therapeutic drug monitoring could optimise the achievement of pharmacokinetic objectives associated with an effective antibiotic therapy. These data also suggest, that, for most patients, the recommended doses of imipenem at 1 g three times a day and amikacin at 20 to 25 mg/kg, do not achieve the pK targets reported in the literature.

Disclosure of interest

The authors declare that they have no conflict of interest.

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