Pharmacy Research UK

Royal Brompton & Harefield NHS Foundation Trust

A lifetime of specialist care

Do adults with extracorporeal membrane oxygenation (ECMO) have altered pharmacokinetic profiles to commonly used anti-infectives - caspofungin, posaconazole and voriconazole?

Ms Haifa Lyster

Royal Brompton & Harefield NHS Foundation Trust

This report presents research funded by Pharmacy Research UK (PRUK). The views expressed in this report are those of the authors and do not necessarily represent the views of PRUK.

1. BACKGROUND AND HYPOTHESIS

1.1 BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is an advanced life support system which allows for prolonged cardiopulmonary support in patients with life-threatening respiratory or cardiac failure (1, 2). It can be used as a bridge to either lung or heart transplantation, or to a long-term ventricular assist device. There are 2 types of ECMO – Venoarterial (VA) or Venovenous (VV) (3); in both the blood is drained from the venous system and oxygenated outside the body. In VV ECMO the blood is returned to the venous system; this is driven by the patients' own heart function, hence maintaining pulsatile blood flow, and provides respiratory support only. While in VA ECMO the blood is returned to the arterial system bypassing both the heart and the lungs so it can be used for supporting both respiratory and cardiac failure. In both modalities, blood is drained from the venous system. In VA ECMO it is returned to the arterial system, and in VVECMO it is returned to the venous system. Critically ill patients will often have a number of organ dysfunctions requiring support including mechanical ventilation and renal replacement therapy. These therapies together with the patients' underlying pathophysiological conditions are known to affect the pharmacokinetics (PK) of many drugs, such as the volume of distribution (Vd) and clearance (Cl) (3, 4). Where Vd refers to the volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in the plasma; and Cl is the volume of plasma cleared of drug per unit time by the processes of metabolism and excretion.

Essentially, ECMO may alter the PK in a number of ways which include sequestration of the drug by the ECMO circuit (5, 6), increasing the Vd, alteration in renal and liver blood flow, altered plasma protein binding and decreased drug elimination. The impact of these PK changes can lead to either therapeutic failure or toxicity. The physicochemical properties of the drug will determine to what extent its PK is altered; in that those lipophilic drugs are significantly sequestered in the circuit while hydrophilic drugs are significantly affected by hemodilution. Hence, the ECMO system itself may induce PK changes in a critically ill patient who already exhibits altered PK; the independent effects of ECMO add to the complexities in this group and are difficult to quantify.

Common mechanisms by which ECMO may alter PK include increased volume of distribution (Vd), drug adsorption in circuits and decreased drug elimination. Factors affecting PK on ECMO are summarised in Fig 2. Renal replacement whilst on ECMO adds increasing

complexity to the PK of drugs because the presence of two extracorporeal circuits can make the estimation of PK parameters more difficult.

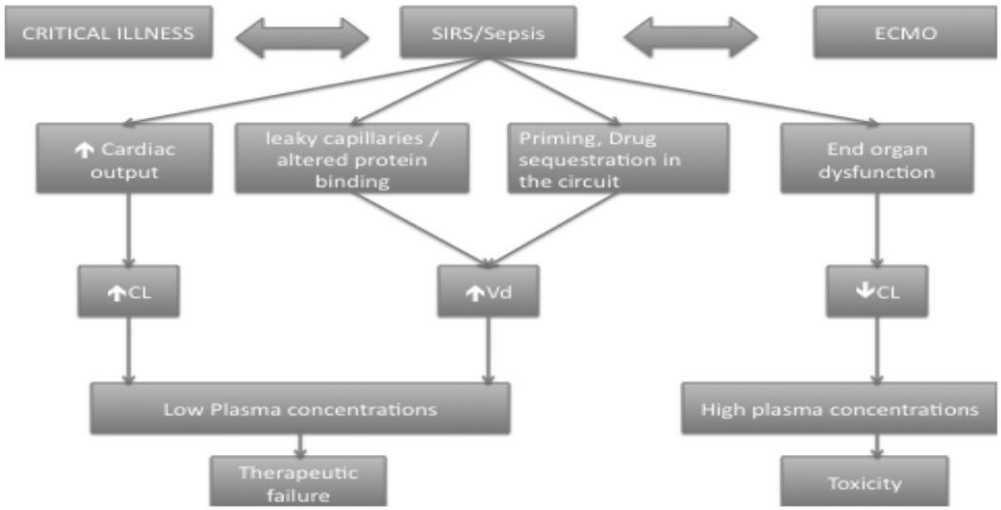


Figure 1. Impact of Critical illness, inflammation, ECMO on drug pharmacokinetics (submitted for publication Shekar *et al*). Vd volume of distribution), CL (clearance), SIRS (Systemic Inflammatory Response Syndrome).

1.2 PRE-CLINICAL DATA / CLINICAL DATA

There are a number of PK studies in patients with ECMO; the majority were performed in neonates and showed significant changes in the PK of antibiotic, sedative and analgesic drugs. These results cannot be extrapolated to adults as the physiologic processes that affect absorption, distribution, metabolism and excretion have not fully developed and are thus different to those in adults.

While the use of diuretics, anticoagulation, sedative, inotrope and vasopressor agents can be titrated to a measurable pharmacodynamic (PD) end-point, the use of anti-infectives cannot. The application of PK principles in both selecting the appropriate anti-infective and its dosage regimen is important in optimizing outcome. Changes in antibiotic PK can lead to either therapeutic failure or toxicity in the patient; however, the potential emergence of resistant bacteria or fungi has wider implications to future management of these infections at a time where there is paucity in newer anti-infective agents available.

There are a few case studies or small studies in adult patients with ECMO which have investigated vancomycin(7), oseltamavir(8-10), voriconazole(11, 12) and caspofungin(11, 12); their conclusions are preliminary. They conclude with a recommendation of tailored dosing using therapeutic drug monitoring, however, not these drugs have their blood levels routinely measured e.g. caspofungin.

An ex-vivo study investigated the influence of plasma protein binding on sequestration in the ECMO circuit and concluded that for drugs with similar lipophilicity, the extent of protein binding may determine the degree of circuit loss(13). It would be anticipated that both caspofungin and posaconazole would be prone to sequestration as they are both highly lipophilic and/or have a high degree of protein binding.

Figure 2:

Lipophilicity (Log P)	
Highly Lipophilic >5	Posaconazole
Lipophilic >1	Voriconazole Chloramphenicol Vancomycin
Neutral -1 -+1	Micafungin Linezolid Caspofungin Ceftriaxone Ciprofloxacin Meropenem Aciclovir
Hydrophilic <-1	Ceftazidime Gentamicin Piperacillin-Tazobactam Ganciclovir

Protein binding (%)	
>90%	Micafungin Posacoanzole Caspofungin Ceftriaxone Teicoplanin
50-90%	Voriconazole Vancomycin Chloramphenicol
10-50%	Aciclovir Linezolid Gentamicin Piperacillin-Tazobactam Ciprofloxacin
<10%	Ceftazidime Ganciclovir Meropenem

Currently there are no guidelines for dosing of drugs in patients with ECMO. The use of standard dosing in these critically ill patients can lead to sub-optimal outcomes, and ideally dosing should be individualized through the use of therapeutic drug monitoring.

There is a multi-centre, open label, descriptive PK study currently recruiting – ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation(14). This research will add to the evidence base for dosing in this group of patients. The Physiological Based Pharmacokinetic model for an adult ECMO patient will be invaluable in predicting how these patients will handle other drugs in the future.

Anti-infectives are commonly administered to critically ill patients on the intensive care unit, including those with ECMO. The antifungals: voriconazole, posaconazole and caspofungin are within the first- and second-line fungal infection treatment guidelines at the Royal Brompton & Harefield NHS Trust. These include fungal infections such as aspergillus and candida which can cause life-threatening sepsis. Hence, they are chosen as the first group of drugs to be studied to determine changes in their PK, which could lead to robust dosing guidelines in this group of patients.

Our proposed study will provide critical PK data to guide clinicians in administering "the right dose of the right drug, at the right time" during ECMO.

1.3 HYPOTHESES TO BE INVESTIGATED

ECMO significantly alters the PK of anti-infectives, which include posaconazole, voriconazole and caspofungin, thereby contributing to an elevated risk of therapeutic failure, drug toxicity and emergence of microbial resistance in critically ill adult patients on ECMO.

2 AIMS AND OBJECTIVES

2.1 STATEMENT OF AIMS

To study whether adult patients with extracorporeal membrane oxygenation (ECMO) have altered pharmacokinetic profiles to commonly used anti-infectives, including caspofungin, posaconazole and voriconazole?

2.2 OBJECTIVES

a) Determine the degree of sequestration of the commonly used anti-infectives: posaconazole, voriconazole and caspofungin in the ECMO circuit
b) Develop a physiologic based pharmacokinetic (PBPK) model for adult patients with ECMO

3 METHOD

3.1 EX-VIVO MODELLING OF DRUG LOSSES ON ECMO – TO DETERMINE DRUG SEQUESTRATION IN THE ECMO CIRCUIT

ECMO circuits were set up as per the standard protocol for adult patients on ECMO and were primed with whole human blood, sodium chloride 0.9% and Human Albumin Solution 20% with a final volume of approximately 700-750ml; then the investigated drug was added. In the case of caspofungin, 3.75mg was added to achieve 5mg/L concentration; posaconazole 3mg was added to achieve a concentration of approximately 4mg/L and for voriconazole 4mg was added to achieve 6mg/L concentration.

The ECMO circuits were maintained at a flow-rate of 4-5L/min, at physiological pH and temperature for 24 hours. Control samples (2ml) were withdrawn and stored in PET vacutainer tubes in a water bath at 37^0C. Serial samples (2ml) were collected at baseline, 30, 60, 120 and 360mins and at 12 and 24 hours; the concentrations of voriconazole and posaconazole were quantified using HPLC-mass spectrometry and caspofungin using a HPLC assay with fluorescence detection. The experiments were repeated four times for each

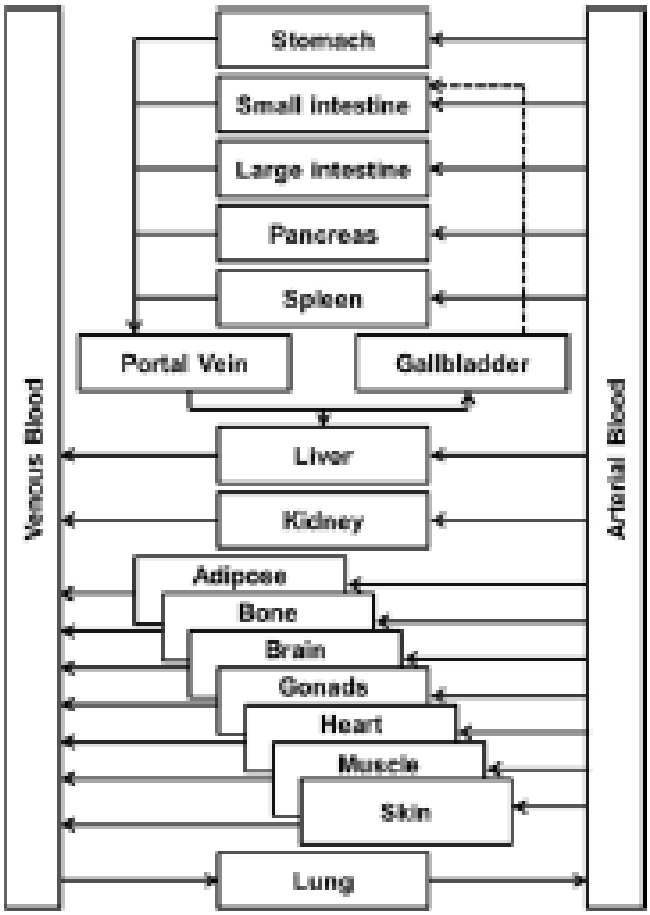
caspofungin and posaconazole and twice for voriconazole and mean drug concentration vs time graph plots were drawn.

Figure 3: an example of the blood-primed ECMO circuit used

3.2 BUILD A PHYSIOLOGIC BASED PHARMACOKINETIC (PBPK) MODEL FOR A CRITICALLY ILL PATIENT WITH ECMO

PBPK modelling offers a mathematical modelling framework for integrating mechanistic data on absorption, distribution, metabolism and excretion to predict the time course of synthetic or natural chemical substances in humans(15, 16). PBPK can predict the pharmacokinetics of a drug based on it physiological and drug-specific data e.g. physicochemical properties, clearance and metabolism. These models are built using compartments or 'building blocks' which represent tissues and organs with their physiological volume and blood flow rates, an example is illustrated schematically as follows (fig.4) (16):

Figure 4: Schematic diagram of a standard PBPK model structure



Distribution of a drug into an organ can be limited by either blood-flow (=well stirred model) or by permeability, this is described by mass balance equations. Ultimately, these models, once validated, can be used to predict the plasma concentration of a drug following intravenous or oral administration. They can determine the dose required in a disease population by scaling or extrapolating from that in a healthy volunteer if the model has the relevant physiological properties of this population incorporated(17).

To develop a simulated PBPK model of a critically ill patient on ECMO support (as a separate compartment) the role of ECMO as an independent variable in a critically ill patient with altered PK can be quantified. The individual effects of renal replacement therapies and ECMO can also be studied; in addition, any differences between the two types of ECMO i.e. VV and VA can be explored.

Develop with collaboration with a number of partners: Certara (Dr Farzaneh Salem and Dr Trevor Johnson) in Sheffield, UK, Dr Jerry Campbell and Dr Harvey Clewell previously of The Hamner Institute, Durham, North Carolina and Dr Kevin Watt, University of North Carolina, Durham, NC.

4 RESULTS

4.1 EX-VIVO EXPERIMENTS

Figure 5. shows that there is a mean loss of 63% in posaconazole concentration in the ex-vivo ECMO model compared with 11% in the control samples over 24 hours ($p<0.005$).

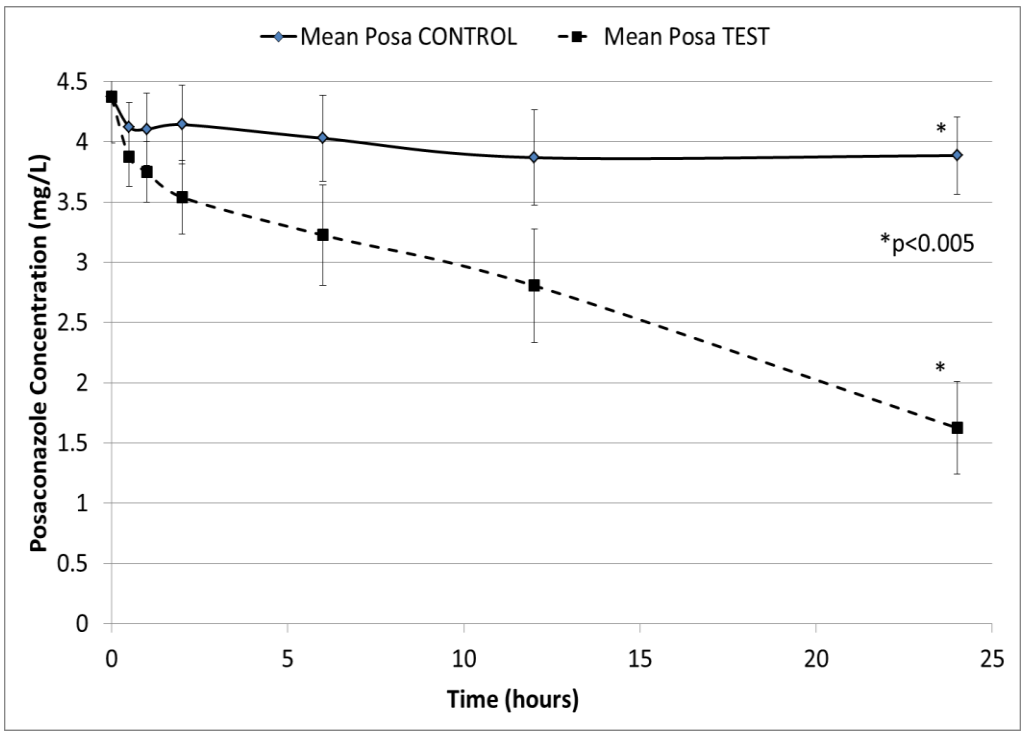


Figure 6. Mean voriconazole concentration vs time plot over 24 hours in blood-primed ECMO circuit showed a mean loss of 27% in the ex-vivo ECMO model compared with 19.2% in the control sample ($p<0.05$)

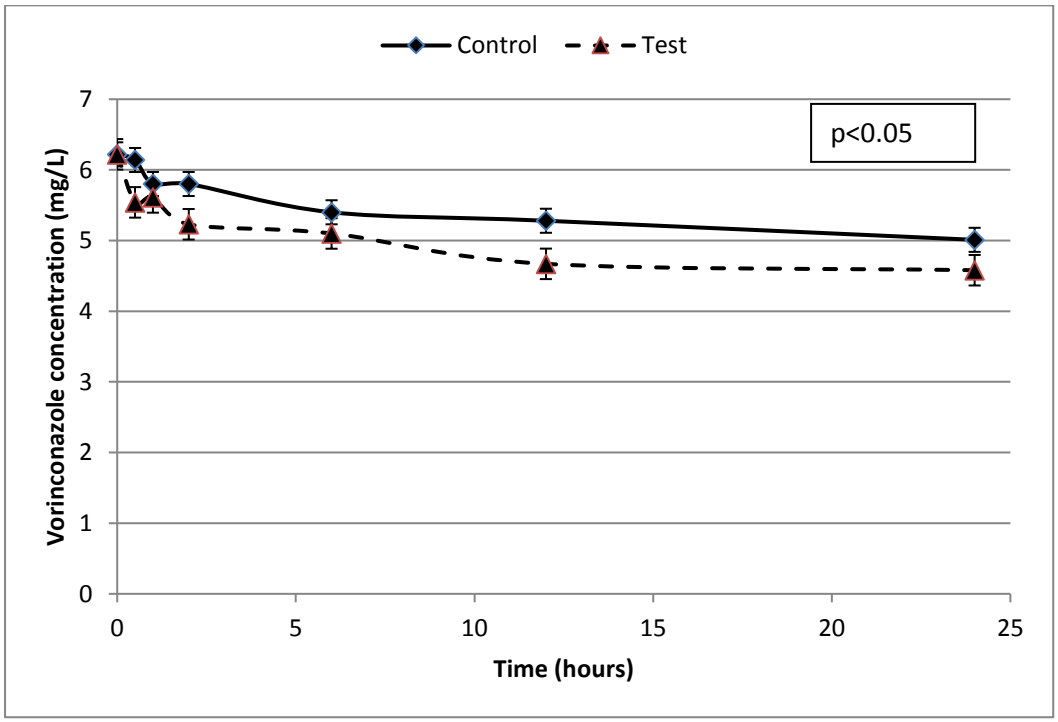
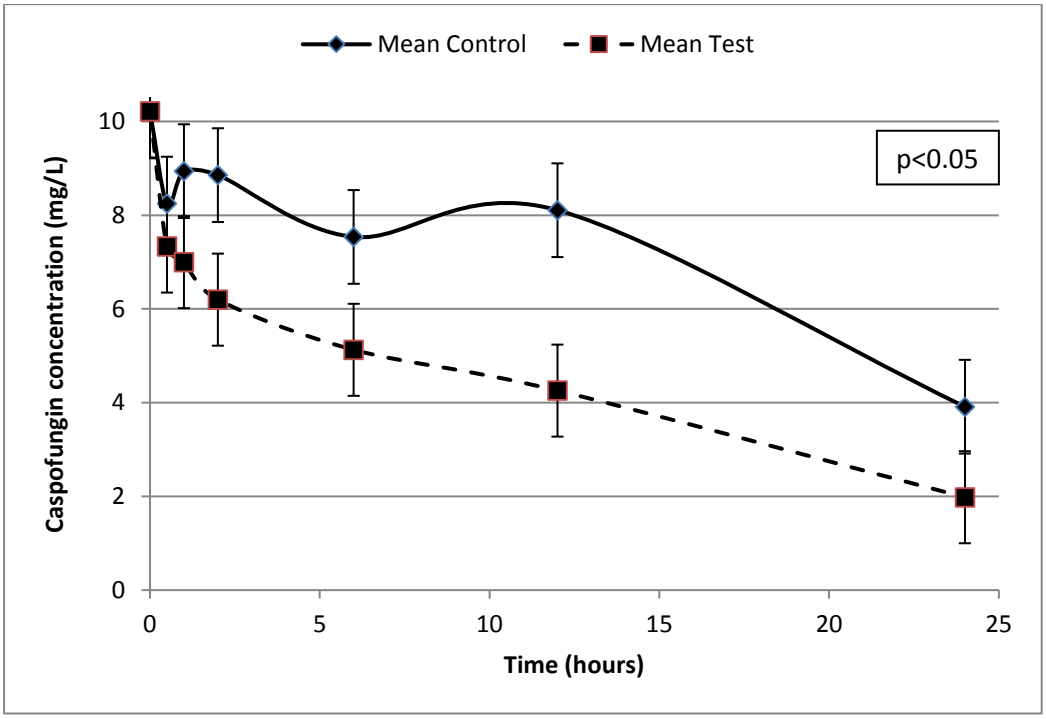


Figure 7. Mean caspofungin concentration vs time plot over 24 hours in blood-primed ECMO circuit shows a mean loss in concentration of 80% in the ex-vivo ECMO model compared with 61% in the control samples over 24 hours (p=ns). Mean AUC 40.9±11.9 in blood-primed ECMO circuit compared with 48.03±14.4 in the control (p=0.024)



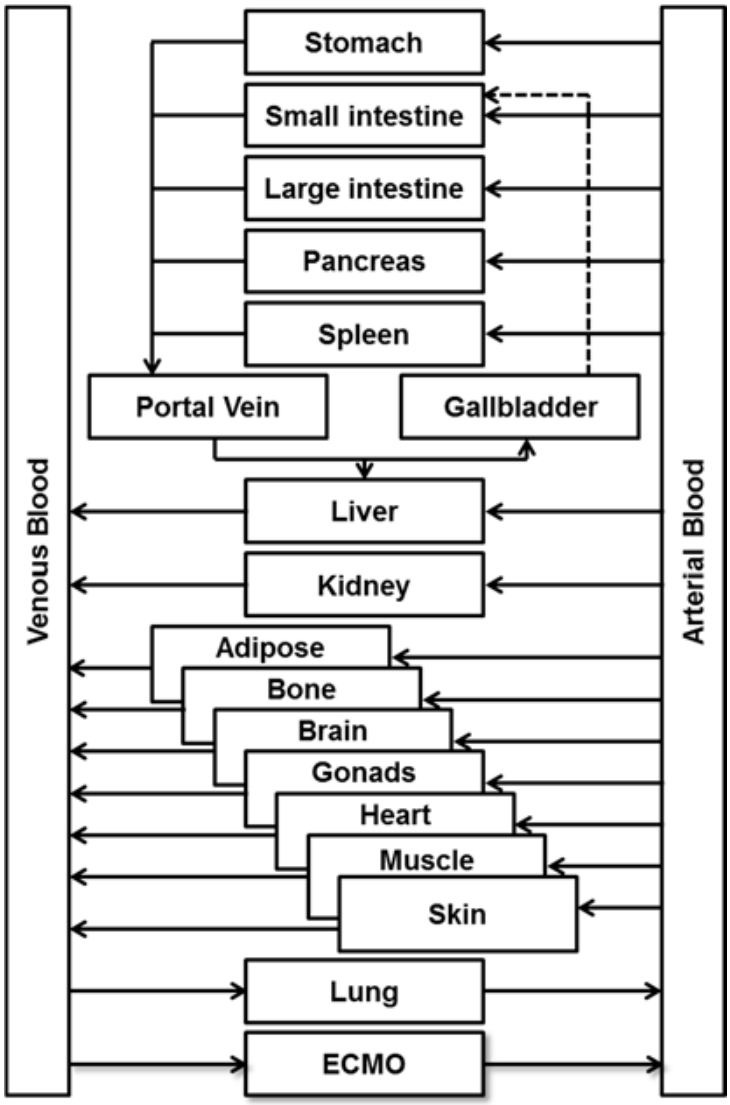
4.2 PBPK MODEL -ECMO COMPARTMENT:

The 'PBPK adult model' consists of the following tissue compartments and corresponding blood flows: adipose, bone, brain, gut, heart, kidney, hepatic (liver) – venous and arterial, lung, muscle, skin, spleen, testes and 'remaining tissue'. An ECMO compartment was added to this 'PBPK adult model' to account for the effect of ECMO on drug distribution e.g. sequestration into the circuit. This ECMO compartment has been assigned a volume (700-750ml) and an equal blood flow (4-5L/min) into and out of the compartment derived from the volume and flow rates used in the ex-vivo experiments. The degree of caspofungin, posaconazole or voriconazole sequestration has been informed from the ex-vivo experiments (% loss over time from figs 5-7) to define the ECMO compartment. The physicochemical and in-vitro data (from literature and Drugbank) of the 3 drugs used for the individual drug PBPK model are shown in table 1.

Table 1: Physicochemical and in-vitro data used for the PBPK models

	VORICONAZOLE	POSACONAZOLE	CASPOFUNGIN
Physicochemical properties			
Lipophilicity (Log P)	1.8	5.5	0
Mol Wt (g/mol)	349.3	700.98	1093.31
Protein binding (%)	58	>98	97
Fraction unbound (Fu) %	4.8		3.5
pKa (strongest acidic)	12.71	14.83	8.75
pKa (strongest basic)	2.27	3.93	9.76
Vd	4.6L/kg	1774L	N/A
Metabolim and elimination			
Renal Clearance	0.096L/hr <2% unchanged	<0.2% unchanged	0.0018ml/min/kg 1-2% unchanged
Ka (1/hr)	0.849		
Transporters/ Hepatic enzymes	CYP – 2C19, 2C9 and 3A4	Pgp UDP glucouronidation	OATP1B1 0.15ml/min/kg
Vmax (pmol/min/mg protein)	40±13.9		
Km (µM)	9.3±3.6		
Plasma clearance		7.3L/hr	10-12ml/min
Half-life (hrs)	N/A (non-linear kinetics)	35 (20-66)	9-11

Figure 8: PBPK model structure with ECMO compartment*



*Watt, K. (2016). *Physiologically-based Pharmacokinetics in Critically Ill Children*

NB this model will need to be optimised and validated with in-vivo PK data from critically ill patients on ECMO (EAT-PK study, which is the next and final phase of the project).

5 DISCUSSIONS AND CONCLUSIONS

5.1 DISCUSSION

Both posaconazole and caspofungin exhibited significant loss in concentration in the ex-vivo ECMO circuit primed with whole human blood, suggesting that therapeutic concentrations of posaconazole and caspofungin cannot be guaranteed in patients on ECMO. However, while voriconazole exhibited significant loss in concentration in the ex-vivo ECMO circuit primed with whole human blood compared to the control, this was not as marked as with caspofungin and posaconazole.

Where available, therapeutic drug monitoring may be required to guide therapy to ensure therapeutic success, currently at RBHFT only posaconazole and voriconazole assays are clinically available.

The results from the ex-vivo experiments were used to parameterize the drug-specific ECMO compartment in the PBPK model, to enable translation into bedside dosing recommendations once the model is optimised. Both posaconazole and caspofungin are almost completely protein bound, hence hypoalbuminaemia (common in critically ill patients) will need to be considered as a covariate. This model now requires validation and optimising with in-vivo PK data from adult patients on ECMO in the EAT-PK (Does Extra-Corporeal Membrane Oxygenation alter Anti-infectives Therapy PharmacoKinetics in adult critically ill patients?) study which is due to commence soon.

EAT-PK study: in this descriptive study, following informed consent, adult patients with ECMO on caspofungin, posaconazole or voriconazole will be sampled over a single dosing period on the first or second day of ECMO treatment or of an antimicrobial course (7 timed samples in total). Where possible, sampling during one extra dosing interval will occur 4-8 days later while on ECMO treatment and/or prior to the next tubing change.

These optimised PBPK models and our subsequent Population-PK models can form the basis for simulating dosing guidelines for anti-infectives used in patients on ECMO.

The development of a clinically useful Physiological Based Pharmacokinetic model for an adult ECMO patient, which can be extended, will be invaluable in predicting how these patients will handle other drugs in the future.

5.2 SUMMARY OF POTENTIAL BENEFITS TO PATIENTS AND THE NHS

The application of PK principles in both selecting the appropriate anti-infective and its dosage regimen is important in optimizing patient outcome. Changes in antibiotic PK can lead to either therapeutic failure or toxicity in the patient; however, the potential emergence of resistant bacteria or fungi has wider implications to the NHS. Optimal antimicrobial prescription has significant implications not only for the patients on ECMO but also for other ICU patients and the community in general. Optimal dosing of an antimicrobial agent will not only lead to improved microbiological and clinical cure rates in an individual patient, but also will reduce the emergence of resistant organisms. This supports the delivery of the *NICE antimicrobial stewardship guidelines, April 2014.*

Success of appropriate disease modifying drug therapy is crucial for the success of ECMO as it is only a temporary life support technique used until the heart and lungs recover. The choice of the right drug at the right dose as guided by this study may identify practice changes that could result in a significant reduction in number of days spent on the ventilator, overall ICU stay and ICU acquired infections.

5.3 LIMITATIONS:

These models have been developed using in vitro data from the literature, the physicochemical properties of the individual drugs and the loss by sequestration to the ECMO circuit from the ex-vivo experiments. These still need to be optimised and validated using in-vivo patient samples from the EAT-PK study hence will rely on patient recruitment.

Potential limitations are the non-linearity of the PK of voriconazole, also both voriconazole and posaconazole may be administered by both enteral and IV routes and there will be an impact of dose adjustments as per their plasma levels (our standard of care) which will need to be considered. Data from the literature with critically ill patients with no ECMO will act as the control group.

Finally, the ex-vivo experiments were unable to continue beyond 24 hours or mimic multiple dose administrations due to haemolysis in the ECMO circuit, hence these models do not account for any potential saturation of the drugs to the tubing over time.

5.4 CONCLUSIONS

These experiments showed variable degrees of drug sequestration by the ECMO circuit with posaconazole and caspofungin highly sequestered and voriconazole with limited sequestration (albeit a significant difference compared to control), therapeutic drug monitoring may be required to guide therapy. These PBPK models once optimised will form the basis for dosing guidelines for anti-infectives used in patients on ECMO.

6 REFERENCES

1. Bartlett RH. Extracorporeal life support: history and new directions. ASAIO J. 2005;51(5):487-9.
2. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. Minerva Anestesiol. 2010;76(7):534-40.
3. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care. 2012;27(6):741.e9-18.
4. Mousavi S, Levcovich B, Mojtahedzadeh M. A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation. Daru. 2011;19(5):312-21.

5. Shekar K, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care. 2012;16(5):R194.
6. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med. 2010;36(12):2109-16.
7. Mulla H, Pooboni S. Population pharmacokinetics of vancomycin in patients receiving extracorporeal membrane oxygenation. Br J Clin Pharmacol. 2005;60(3):265-75.
8. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Fernandez C, et al. Oseltamivir carboxylate accumulation in a patient treated by haemodiafiltration and extracorporeal membrane oxygenation. Intensive Care Med. 2010;36(7):1273-4.
9. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Corvol E, et al. Impact of extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration on the pharmacokinetics of oseltamivir carboxylate in critically ill patients with pandemic (H1N1) influenza. Ther Drug Monit. 2012;34(2):171-5.
10. Mulla H, Peek GJ, Harvey C, Westrope C, Kidy Z, Ramaiah R. Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support. Anaesth Intensive Care. 2013;41(1):66-73.
11. Ruiz S, Papy E, Da Silva D, Nataf P, Massias L, Wolff M, et al. Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. Intensive Care Med. 2009;35(1):183-4.
12. Spriet I, Annaert P, Meersseman P, Hermans G, Meersseman W, Verbesselt R, et al. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2009;63(4):767-70.
13. Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC, et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care. 2015;19:164.
14. Shekar K, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, et al. ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation: a multi-centre study to optimise drug therapy during ECMO. BMC Anesthesiol. 2012;12:29.
15. Jones HM, Parrott N, Jorga K, Lave T. A novel strategy for physiologically based predictions of human pharmacokinetics. Clin Pharmacokinet. 2006;45(5):511-42.
16. Jones HM, Rowland-Yeo K. Basic concepts in physiologically based pharmacokinetic modelling in drug discovery and development. CPT: Pharmacometrics & Systems Pharmacology. 2013;2(e63):1-12.
17. Jones HM, Mayawala K, Poulin P. Dose selection based on physiologically based pharmacokinetic (PBPK) approaches. Aaps j. 2013;15(2):377-87.

ACKNOWLEDGEMENT: The ex-vivo experiments for caspofungin and posaconazole were supported by a research grant from MSD.