# Potential voriconazole, posaconazole and caspofungin sequestration during extracorporeal membrane oxygenation: results of an ex-vivo experiment

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**Abstract:** (word count 199)

Fungal infections are common and are frequently associated with clinical failure in patients receiving extracorporeal membrane oxygenation (ECMO). Antifungal drugs have physicochemical characteristics associated with a higher likelihood of sequestration onto ECMO circuitry potentially leading to a sub-therapeutic drug concentration. The percentage of sequestration of the antifungal drugs: voriconazole, posaconazole and caspofungin was determined using an *ex-vivo* ECMO model. The circuits were primed with whole human blood, sodium chloride 0.9% and human albumin solution. Serial 2ml samples were taken at baseline, 0.5, 1, 2, 6, 12 and 24 hours after drug addition; these were paired with non-ECMO controls stored in a water bath at $37^0$C. The experiments were repeated four times each for caspofungin and posaconazole and twice for voriconazole. The mean loss from the blood primed ECMO circuits and controls at 24 hours relative to baseline were 27% and 19.2% for voriconazole ($p<0.05$), 80% and 61% for caspofungin (p=ns) and 64% and 11.4% for posaconazole ($p<0.005$). Calculated $AUC_{0-24}$ showed a significant loss over the 24 hours compared to the controls with all 3 drugs, suggesting that therapeutic concentrations of these antifungal agents cannot be guaranteed with standard antifungal dosing in patients on ECMO.

## Background:

Extracorporeal membrane oxygenation (ECMO) is an advanced life support system which allows for temporary cardiopulmonary support in patients with life-threatening respiratory or cardiac failure (1, 2). ECMO does not provide treatment of the underlying illness, it is purely a supportive strategy that is implemented while underlying co-morbidities such as infection are treated i.e. bridge to recovery. It can

also be used as a bridge to either lung or heart transplantation, or to a long-term ventricular assist device. There are many complications associated with ECMO, commonly bleeding, renal failure and infections(3). Infection represents a significant clinical problem in critically ill patients requiring ECMO support as it can be the indication for ECMO e.g. influenza and coronavirus associated respiratory failure or occur as a secondary complication. The prevalence of hospital acquired and bloodstream infections during ECMO ranges from 9 to 65% in adults (4-9). Co-infections commonly are bacterial, but increasingly life-threatening fungal infections such as *Aspergillus spp.* and *Candida spp.* are being observed. Hospital acquired infections in critically ill patients with ECMO are linked with poor morbidity and mortality outcomes (3, 10-12).

Antifungals are often administered to critically ill patients with ECMO. Dose optimisation of anti-infectives can be a significant challenge, with suboptimal dosing contributing to poorer outcomes and the emergence of resistance (13). Critically ill patients frequently have multi-organ dysfunctions requiring extracorporeal support including mechanical ventilation, ECMO and renal replacement therapy (RRT). in particular RRT and ECMO, together with the patients' underlying pathophysiological conditions are known to affect the pharmacokinetics (PK) of many drugs.

ECMO itself may alter the PK in a number of ways, including sequestration of the drug by the ECMO circuit (14, 15), and through cardiovascular changes and altered plasma protein binding, changes to drug volume of distribution and clearance. Such PK changes of anti-infective drugs may lead to either therapeutic failure or drug 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. Currently there are no guidelines for dosing of antifungal drugs in patients with ECMO.

Predicting whether drug concentrations will be affected by ECMO is uncertain, but some authors have hypothesised that the physicochemical properties of the drug may guide the extent that PK are altered. Specifically, lipophilic drugs are considered more likely to be significantly sequestered in the ECMO circuit. Hydrophilic drugs may be significantly affected by hemodilution, particularly in neonates and small infants (16). 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(17). The aim of this pilot study was to determine whether the commonly used antifungals, voriconazole, posaconazole and caspofungin are sequestered in an *ex vivo* ECMO circuit. It is hypothesised that both caspofungin and posaconazole would be prone to sequestration because of high protein binding and/or lipophilicity (Table 1).

## Materials and methods:

Ethics approval from UK National Health Service (NHS) Blood and Transplant was obtained for use of non-clinical whole blood for the blood-primed ECMO circuit experiments. Royal Brompton & Harefield Foundation Trust NHS permission was also granted (R&D ref 2015IC003B). Informed consent was not applicable as no human subjects were enrolled in this study.

### Extracorporeal membrane oxygenation circuits

An ECMO circuit comprising of Levitronix Centrimag blood pump (Chalice Medical Limited, Worksop, UK), Paragon PMP Oxygenator pump (Chalice Medical Limited,

Worksop, UK) and Carmeda bonded tubing (Medtronic, Watford, UK) was set up as per the standard protocol for adult patients on ECMO at our institution (see Figures 1a and 1b, dual circuits set up) maintaining a flow-rate of 4-5 L/min and post-oxygenator pressure between 230-250mmHg measured using a single use post-oxy transducer. By modulating the rate of a sweep gas mix (5.5% carbon dioxide, 12% oxygen and nitrogen balance, BOC, UK) and additional sodium bicarbonate, the system was maintained at physiological pH (7.2-7.5). The Paragon integrated heat exchanger and a heated water bath were used to maintain temperature at $37^0$C throughout the experiment. The circuit was completed with a Carmeda bonded Medtronic soft shell reservoir bag to enable sample withdrawal from the closed circuit.

ECMO circuits were primed with whole human blood (supplied by NHS Blood and Transplant, UK), sodium chloride 0.9% and human albumin solution 20% (Bio Products Laboratory, Radlett, Borehamwood, UK) with a final volume of approximately 700-750ml; then a single drug was added per run.

In the case of caspofungin (Merck Sharp & Dohme Ltd, Hoddesdon, Hertfordshire, UK), 7.5mg was added to achieve 10mg/L concentration; posaconazole (Merck Sharp & Dohme Ltd, Hoddesdon, Hertfordshire, UK), 3mg was added to achieve a concentration of approximately 4mg/L and for voriconazole (Pfizer Ltd, Sandwich, Kent, UK) 4.5mg was added to achieve 6mg/L concentration.

**Sampling**

Serial 2ml samples were taken at baseline, 0.5, 1, 2, 6, 12 and 24 hours after drug addition from a post-oxygenator port; the experiments were repeated four times each for caspofungin and posaconazole and twice for voriconazole. In all experiments

paired non-ECMO control samples were withdrawn from the ECMO circuit at baseline then stored in polyethylene terephthalate (PET) vacutainer tubes in a water bath at $37^0$C with tubes removed at each time point as the test samples to understand natural degradation of the drug over time.

**Antifungal drug assays**

The concentrations of voriconazole and posaconazole were quantified using 2-Dimensional TurboFlow™ high performance liquid chromatography, tandem mass spectrometry (2D HPLC-MS/MS). Range of linearity was from 0.039 -10 mg/L for both voriconazole and posaconazole. The inter-assay variation (CV%) was ≤3.4%. over 0.156 to 10mg/L for voriconazole and ≤3.7% over 0.156 to 10mg/L for posaconazole. Caspofungin concentrations were analysed using a HPLC assay with fluorescence detection, the CV% was <10.3% over the concentration range 0.25 – 10 mg/L in plasma and the limit of detection was 0.0125 mg/L.

**Analysis**

Samples were assayed in triplicate for voriconazole and posaconazole and singlicate for caspofungin. All drug concentrations were referenced to the baseline measurement and plotted as concentration versus time. Data are expressed as mean (±sd); $AUC_{0-24}$ was calculated using the trapezoidal method; MS Excel was used for all the analyses. Any correlation between the drug sequestered and the drug's Log P and degree of protein binding (%) was explored graphically.

**Results:**

The pH, $PaCO_2$ and bicarbonate in all the blood-primed *ex-vivo* circuits were maintained within physiological conditions over 24 hours by titrating sweep gas flow and addition of sodium bicarbonate 8.4% (5-10ml over 24 hours) as required. The

drug concentration-time profiles from 0-24 hours in the *ex-vivo* circuits and controls are presented in Figure 2.

The mean loss from the blood-primed ECMO circuits and controls at 24 hours relative to baseline were 27% and 19.2% for voriconazole ($p<0.05$), 80% and 61% for caspofungin (p=ns) and 63.6% and 11.4% for posaconazole ($p<0.005$).

The $AUC_{0-24}$ was significantly lower in the ECMO circuits compared with the controls for all three drugs (Table 2).

Figures 3a and 3b visually present the relationship of the lipophilicity and protein binding of the three drugs with percentage of drug remaining in the circuit at 24 hours; increased loss was associated with higher degree of protein binding.

**Discussion:**

Antifungals are often administered to critically ill patients with ECMO, suboptimal dosing is associated with poorer patient outcomes and emergence of resistance(13). ECMO may alter drug PK in a number of ways which include sequestration of the drug by the ECMO circuit (14, 15), increasing the volume of distribution, 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. Ex-vivo studies explore the potential and degree of sequestration which is influenced by the drug's physicochemical properties such as lipophilicity and degree of protein binding and ECMO circuit factors e.g. oxygenator, tubing. This ex-vivo study demonstrated that the commonly used antifungals, posaconazole, caspofungin and voriconazole exhibited loss over 24 hours to varying degrees. The mean losses

were 27% and 19.2% for voriconazole ($p<0.05$), 80% and 61% for caspofungin (p=ns) and 63.6% and 11.4% for posaconazole ($p<0.005$).

This is the first report of an ex-vivo study with Posaconazole, it exhibited significant loss in concentration in the *ex-vivo* ECMO circuit primed with whole human blood (Figure 2A) which supports our hypothesis that this loss may be as a result of sequestration into the ECMO circuit. Consequently, therapeutic concentrations of posaconazole may not be guaranteed in patients on ECMO; therapeutic drug monitoring and possibly dose escalation may be required.

With regards to caspofungin (Figure 2B) our results are similar to that of Shekar *et al* which showed a recovery of 56% compared with 99% in control at 24 hours (17). There was some loss in both the control and test samples; further investigation into whether this is an assay issue or adsorption to the tubing and the vacutainer tubes is required. In addition, this continued loss of caspofungin over the 24 hour period and in the controls may suggest that drug degradation or metabolism via plasma peptidases may have occurred (18).

In the case of voriconazole (Figure 2C) there was a smaller loss over the 24 hour period compared with posaconazole and caspofungin; this is to be expected as voriconazole is not as lipophilic or protein bound as posaconazole and caspofungin (Table 1). In our experiments, voriconazole showed a loss of 27% in the ECMO model *vs* 19.2% in controls; this is in contrast with previously published studies (19-21). Different materials in the oxygenators, tubing and pumps have all been shown to have variable impacts on drug sequestration (22). Mehta *et al,* reporting a voriconazole loss of 71% vs 14.8% at 24 hours, used older style ECMO circuits with a1.5-$m^2$ silicone membrane oxygenator (Medtronic) and a custom neonatal tubing

with ¼-inch diameter and 3/32-inch thickness, made of polyvinyl chloride and superTygon (Medtronic). PK changes are both drug and circuit dependent with lipophilic drugs showing greater loss to silicone membranes, as used in the Mehta *et al* experiments, compared with polypropylene ones (23, 24). Raffaeli *et al* also demonstrated greater adsorption to silicone-based membranes compared to the newer generation poly-methyl-pentene (PMP) hollow fibre oxygenators like ours (25). Additionally, differences in the tubing (PVC *vs* heparin-bonded)(26, 27) and pump type (roller *vs* centrifugal pump)(15) all have variable impacts on drug sequestration; these may have influenced the differences in loss seen. *Cies et al* demonstrated a significant loss of voriconazole in the ECMO circuits with an oxygenator in the series and no significant loss without one(19). Our results are comparable to their circuits without an oxygenator, also of note is the oxygenator used in their circuits is different, polypropylene compared to PMP, but the heparin-bonded tubing was similar. A recent study by *Raffaeli et al* explored the extraction of voriconazole by the Xenios/Novalung ECMO circuits, finding the mean percentage recovery of 20% at 24 hours (21). The discrepancy between these results illustrate the importance of understanding how the different ECMO circuit components influence the drug-circuit interactions and thus the degree of drug loss.

Voriconazole, posaconazole and caspofungin have different degrees of lipophilicity (log P = 1.8, 5.5 and 0 respectively) and protein binding (58%, >98% and 97% respectively). Shekar *et al* concluded that protein-bound drugs appear to be more significantly sequestered in *ex-vivo* ECMO circuits(17); our results support this with caspofungin and posaconazole showing significant loss compared with voriconazole. Posaconazole exhibited the greatest loss to the ECMO circuit correlating with both high lipophilicity and protein binding of the drug.

In the cases of voriconazole, posaconazole and caspofungin, it is the ratio of the 24-hour area under the drug concentration curve to the MIC (AUC/MIC) PK-PD index which best describes the antifungal activity of all 3 antifungals. In addition echinocandins also demonstrate a concentration dependent PD characteristic ($C_{max}$/MIC)(28). The calculated $AUC_{0-24}$ of the three drugs (see Table 2) showed a significant loss over the 24 hours compared to the controls, suggesting that the PK-PD index may become increasingly unfavourable over time. However, more studies are required to determine whether this change is clinically relevant given the intrinsic PK variability of these drugs and to explore sequestration beyond 24 hours with regular dosing.

Study limitations

This was a pilot study with a small number of experiments, limited by the feasibility and expense of conducting these experiments. The study did not aim to describe the mechanism of interaction between the drugs and an ECMO patient but to determine any potential drug loss over the 24 hour period within the circuit. The effect of individual circuit components on the drug concentrations is beyond the scope of this study.

**Conclusion:**

The results of this study combined with preceding studies suggest that ECMO reduces concentrations of the study antifungal agents. This raises concerns for the ability to deliver efficacious and safe dosing in critically ill patients receiving ECMO. Further study is recommended to define appropriate empiric drug dosing regimens as well as the need for TDM. The PK of these drugs during ECMO may have important clinical implications for patient outcomes and safety.

## Supplementary materials

None


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None.


## Author contributions

Conceptualization: HL, AR, JR, JM, DB, AS; Formal Analysis: HL; Data Collection and statistical analyses; HL; Data Interpretation, HL, DB, JM, JR, AS; AR All authors contributed to drafting and critical review of the manuscript. All authors approved the manuscript for submission

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Determinants of drug absorption in different ECMO circuits. Current drug metabolism. 2012;13(6):767-77.
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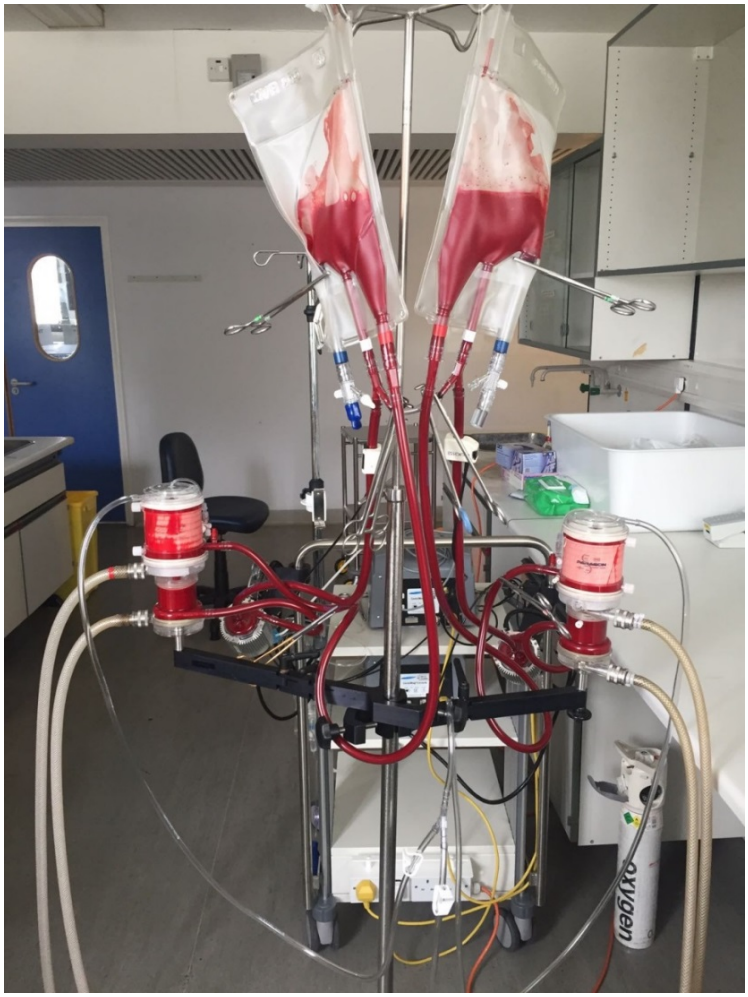
**Tables and figures**

Figure 1a Example of the blood-primed ECMO circuit used Figure 1b Simplified schematic of extracorporeal membrane oxygenation (ECMO) circuit



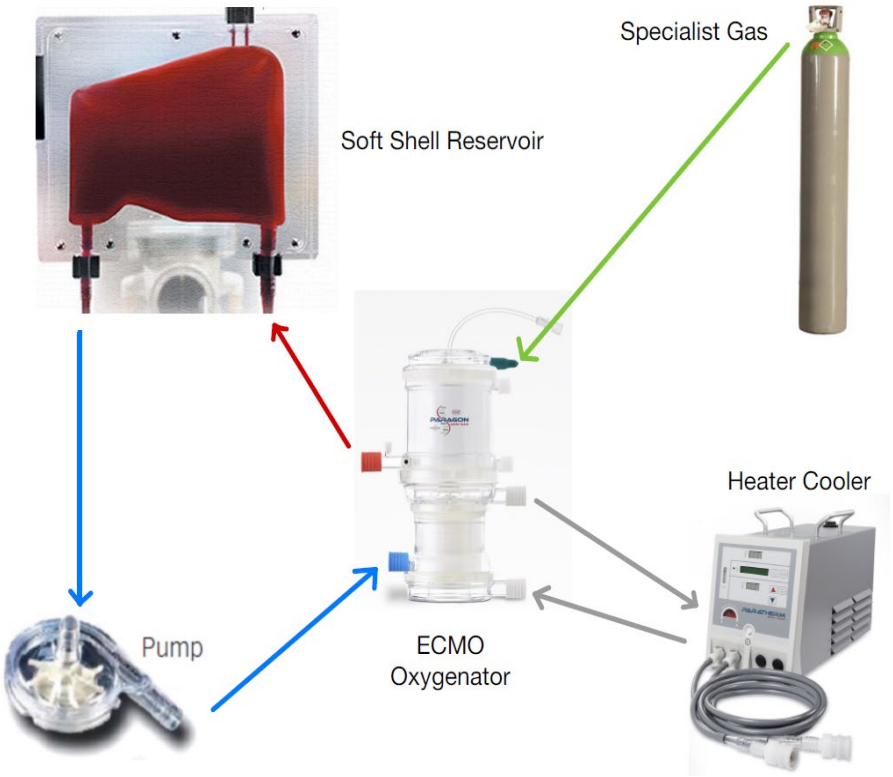
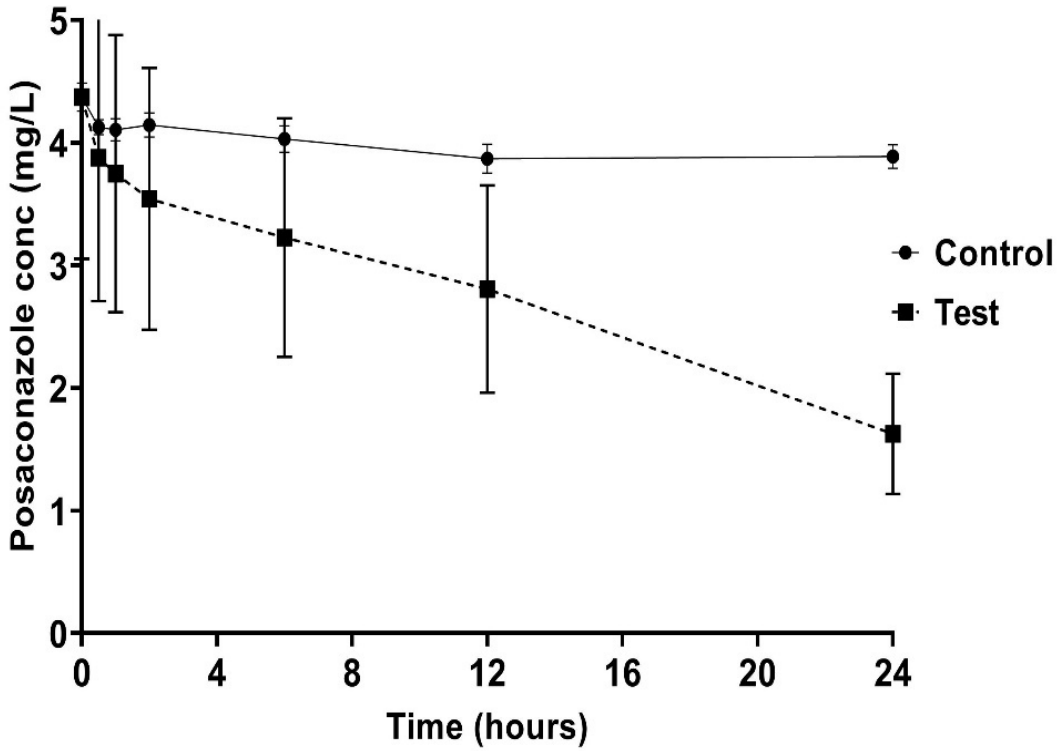

Specialist Gas
Soft Shell Reservoir
Heater Cooler
Pump
ECMO
Oxygenator

Figure 2: Mean concentration of drug remaining in *ex-vivo* ECMO circuits and controls plotted against time (over 24 hours) for posaconazole, caspofungin and voriconazole (error bars indicate standard deviation)

A. Posaconazole

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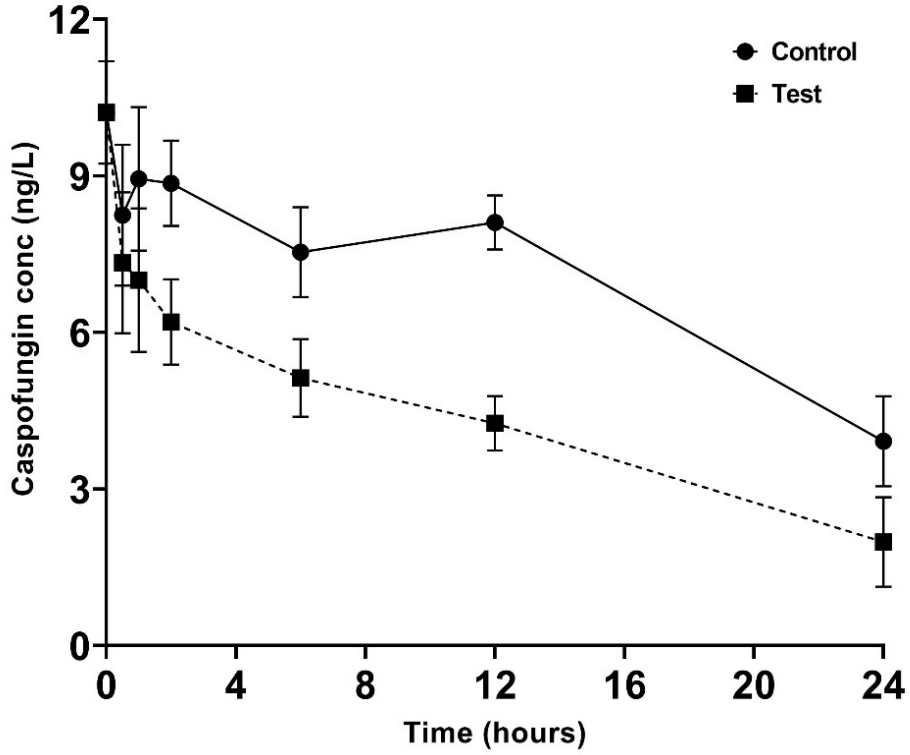



C. Voriconazole

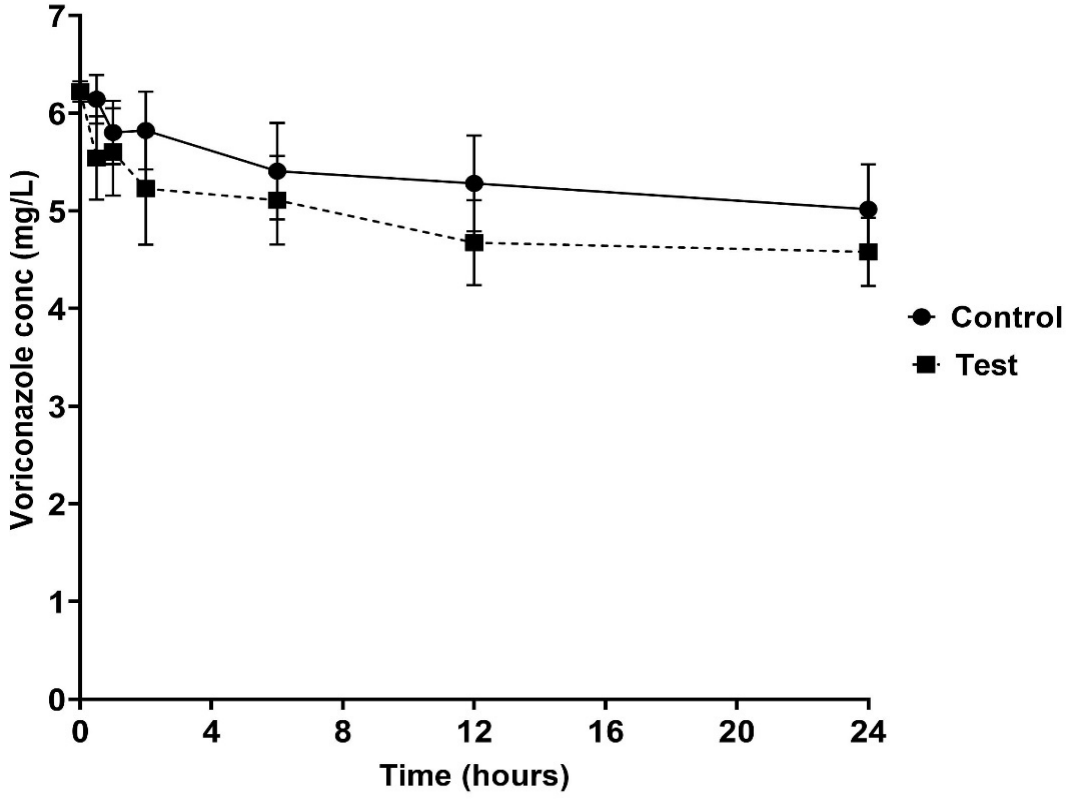


Table 1: The lipophilicity or Log P (the partition coefficient between 1-octanol and water) values and the protein binding characteristics for the individual anti-infective drugs used, these were obtained from the DrugBank online database (29)

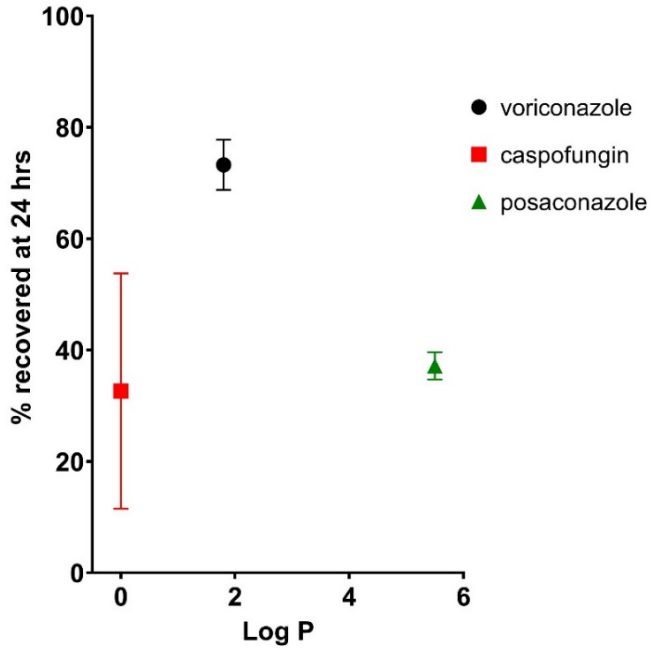
| **Study drug** | **Lipophilicity (logP)** | **Protein binding (%)** |
|---|---|---|
| Voriconazole | 1.8 | 58 |
| Posaconazole | 5.5 | >98 |
| Caspofungin | 0 | 97 |

Table 2: Calculated $AUC_{0-24}$ in the control compared with test ECMO circuits

| **Drug** | **$AUC_{0-24}$– control $mgL^{-1}$ hr** | **$AUC_{0-24}$ – test drug $mgL^{-1}$ hr** | **p-value** |
|---|---|---|---|
| Voriconazole | 32.845±3.7 | 30.81±5.2 | 0.03 |
| Posaconazole | 21.1±1.4 | 22.9±1.3 | <0.0005 |
| Caspofungin | 48.0±14.4 | 40.9±11.9 | 0.02 |

Figure 3: Percentages of drug remaining in *ex-vivo* ECMO circuits and controls plotted against time (over 24 hours) (a) Lipophilicity expressed as a log partition coefficient (log P) values (b) protein binding expressed as percentage.

(a)




(b)