Ex vivo characterisation of effects of renal replacement therapy modalities and settings on pharmacokinetics of meropenem-vaborbactam

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Background

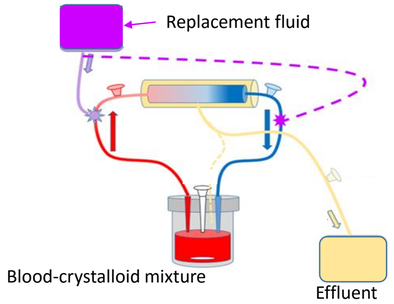
- Meropenem/vaborbactam (Vabomere®) is a novel agent with activity against KPC-producing carbapenem resistant Enterobacteriaceae (CRE)[1]
- Vabomere® is now approved (FDA, 2017) for the management of complicated urinary tract infections.
- Ongoing trials show promising advantages for KPC-producing CRE infections[2]
- CRE infections are severe predisposing patients for sepsis and acute kidney injury requiring renal replacement therapy[3]

Aims

- To estimate the extent of adsorption of meropenem and vaborbactam within a clinically used continuous venovenous hemofiltration (CVVH) circuit system
- To describe the effect of point of dilution and a range of common CVVH settings on the extracorporeal removal of meropenem and vaborbactam.

Methods

***Ex vivo* CRRT model**



$$\left(\begin{matrix}\%\ drug\\ lost\ by\\ degradation\end{matrix}\right) = \left(1 - \frac{\begin{matrix}Measured\\ Concentration\end{matrix}}{\begin{matrix}Initial\\ Concentration\end{matrix}}\right) \times 100$$

$$\left(\begin{matrix}\%\ drug\\ remaining\end{matrix}\right) = \left(\frac{Measured\ Concentration}{Initial\ Concentration}\right) \times 100$$

$$\left(\begin{matrix}\%\\ Adsorbed\end{matrix}\right) = 100 - \left(\begin{matrix}\%\ drug\\ remaining\end{matrix}\right) - \left(\begin{matrix}\%\ drug\ lost\\ by\ degradation\end{matrix}\right)$$

$$\left(\begin{matrix}Extracorporeal\\ clearance\end{matrix}\right) = \frac{\left(\begin{matrix}Effluent\ drug\\ concentration\end{matrix}\right)}{\left(\begin{matrix}Mixing\ chamber\\ drug\ conentration\end{matrix}\right)} \times \left(\begin{matrix}Effluent\\ Flow\ Rate\end{matrix}\right)$$

$$\left(\begin{matrix}Sieving\\ Coefficient\end{matrix}\right) = \frac{Effluent\ drug\ Concentration}{\left[\left(\begin{matrix}Prefilter\\ plasma\\ concentration\end{matrix}\right) + \left(\begin{matrix}Postfilter\\ plasma\\ concentration\end{matrix}\right)\right]/2}$$

Results

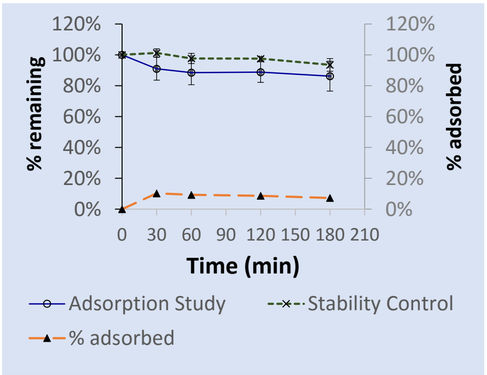


Figure 1. Adsorption of meropenem onto AN 69 filter. Comparison with stability over 3 hours at 37°C.

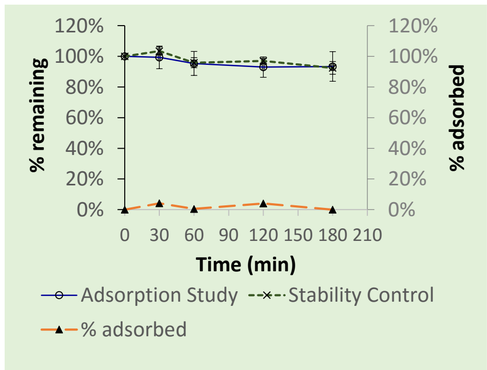


Figure 2. Adsorption of 50 mg/L vaborbactam onto AN 69 filter Comparison with stability over 3 hours at 37°C.

Table 1. The effect of point of dilution on meropenem/vaborbactam sieving coefficients of AN69 ST100 filter at different blood and effluent flow rate.

Blood Flow Rate (mL/min)	Effluent Flow Rate (L/h)	Sieving Coefficient by drug & point of dilution (mean± SD)			
		Meropenem		Vaborbactam	
		Pre-filter	Post- filter	Pre-filter	Post-filter
200	4	1.05 ± 0.09	1.08 ± 0.17	0.78 ± 0.10	0.83 ± 0.16
	2	1.14 ± 0.12	1.07 ± 0.02	0.88 ± 0.15	0.85 ± 0.12
	1	1.10 ± 0.06	1.07 ± 0.09	0.90 ± 0.14	0.86 ± 0.15
100	4	1.06 ± 0.16	0.97 ± 0.16	0.64 ± 0.39	0.70 ± 0.16
	2	1.01 ± 0.13	1.08 ± 0.14	0.79 ± 0.16	0.78 ± 0.12
	1	1.02 ± 0.12	1.02 ± 0.08	0.80 ± 0.14	0.81 ± 0.10

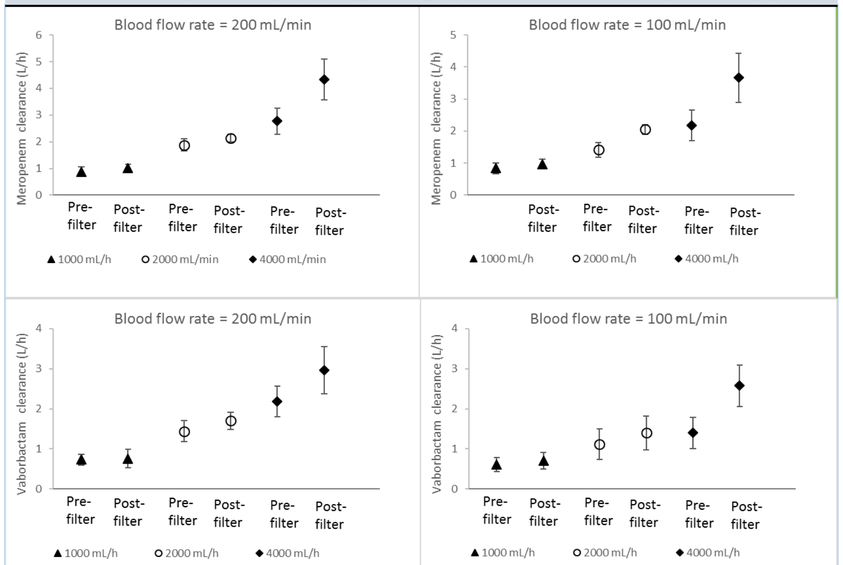


Figure 3. The effect of point of dilution on meropenem and vaborbactam filter clearance (with ST100 filter) at different effluent and blood flow rates.

Conclusions

- No loss of vaborbactam dose due to adsorption compared with minimal loss of meropenem
- Effluent flow rate appears the most important factor affecting meropenem/vaborbactam clearance
- Post filter dilution is associated with increased clearance particularly at high effluent flow rate
- Dosing according to existing meropenem data in CVVH is likely to be sufficient

1) Antimicrob Agents Chemother 2017, 61(11): e01443-17; 2) Open Forum Infect Dis 2017, 4:S534-S535 3)Open Forum Infect Dis 2017, 4(2):ofx063

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