Clearance Measurement in CRRT using Transdermal Fluorescence Detection and Correlation to Antibiotic Pharmacokinetics: *in vivo* Results

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Background / Purpose

Patients undergoing CRRT often have multiple medical conditions, both chronic and acute, requiring different types of treatment, and also are receiving many different drugs. CRRT is a filtering system known to remove some drugs from the bloodstream. Currently, only rough estimates of how much of a specific drug is removed during CRRT are possible. More accurate quantitation would allow determination of whether additional doses or a different dosing regimen was necessary. Thus, there is a need to determine the rate in which different drugs are removed from the bloodstream of a patient undergoing CRRT, in order to improve or adjust the dosing prescription for that drug. Because patients are often receiving multiple different drugs, there is a need to determine the rate of clearance of each drug individually in a single test rather than performing a different test for each drug. Hence we employed the MediBeacon Transdermal GFR Measurement System, with MB-102 as the fluorescent tracer agent, to assess real-time CRRT clearance and the correlation of MB-102 with the antibiotic meropenem.

Objectives

- Establish feasibility of using transdermal fluorescence detection of MB-102 for clearance measurements in CRRT procedures.
- Establish correlation of MB-102 clearance to a drug typically dosed in patients undergoing CRRT.

Methods

The clearance of fluorescent tracer agent MB-102 was followed in an anesthetized nephrectomized pig using both CVVH and CVVHD procedures. Two different blood pump flow rates, low (LBF) and high (HBF), and two different effluent rates were used with each CRRT modality. Continuous measurement of transdermal fluorescence from the pig was complemented by plasma determinations pre and post CRRT filter of MB-102 tracer agent plasma concentration, BUN, and serum creatinine at several time points during each procedure. The antibiotic meropenem was administered to the pig prior to commencement of either CRRT procedure, and meropenem plasma concentrations at several time points were also obtained.

Results

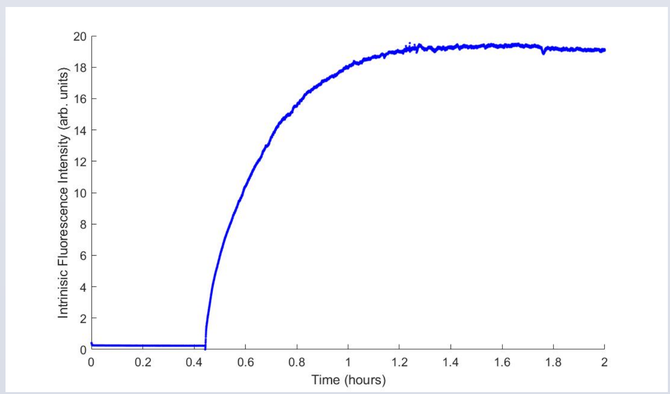


Figure 1: Transdermal fluorescence from MB-102 reaches steady-state in about an hour in bilateral nephrectomized pig. Measurement taken at sternum of the pig.

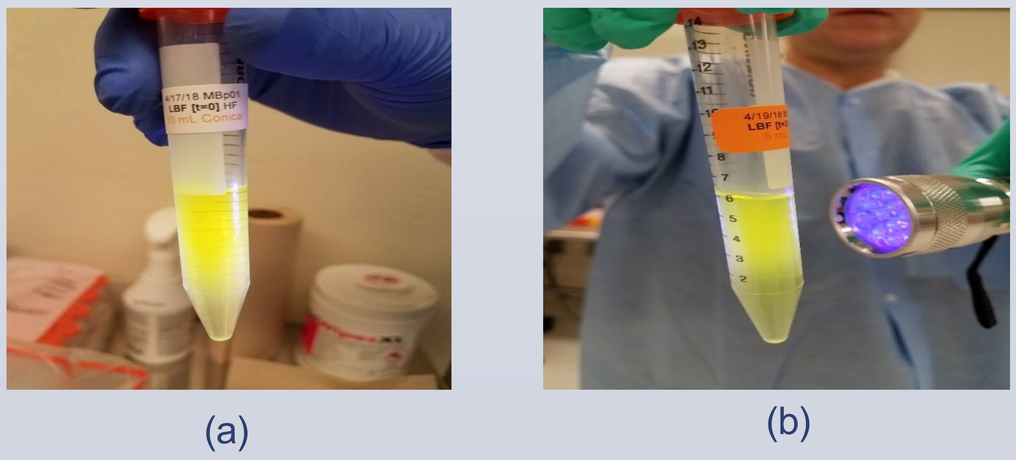
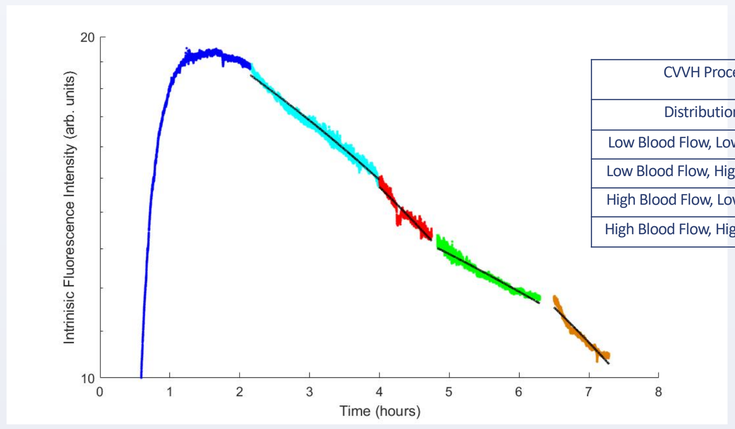


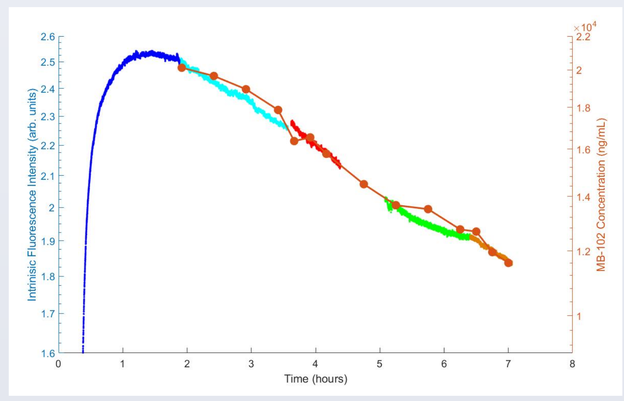
Figure 2: (a) Upon initiation of CVVH, MB-102 is excreted in the ultrafiltrate, seen as the yellowish-green glow with illumination of blue excitation light. (b) Upon initiation of CVVHD, MB-102 is excreted in the spent dialysate, seen as the yellowish-green glow with illumination of blue excitation light.

Results (continued)



CVVH Process	MB-102 Clearance Rate Constant (1/hr)
Distribution •	-----
Low Blood Flow, Low UF Flow •	0.11
Low Blood Flow, High UF Flow •	0.15
High Blood Flow, Low UF Flow •	0.08
High Blood Flow, High UF Flow •	0.12

Figure 3: Decrease in transdermal fluorescence (logarithmic scale) at sternum in a porcine model during CVVH as a function of time, along with calculations of MB-102 clearance rate for the two blood flow rates and two ultrafiltrate flow rates used in the procedure.



Distribution •`
Low Blood Flow, Low SD Flow •
Low Blood Flow, High SD Flow •
High Blood Flow, Low SD Flow •
High Blood Flow, High SD Flow •
Pre HD Plasma Conc. •

Figure 4: Decrease in transdermal fluorescence (logarithmic scale) at sternum in a porcine model during CVVHD as a function of time, with overlay of MB-102 plasma concentration.

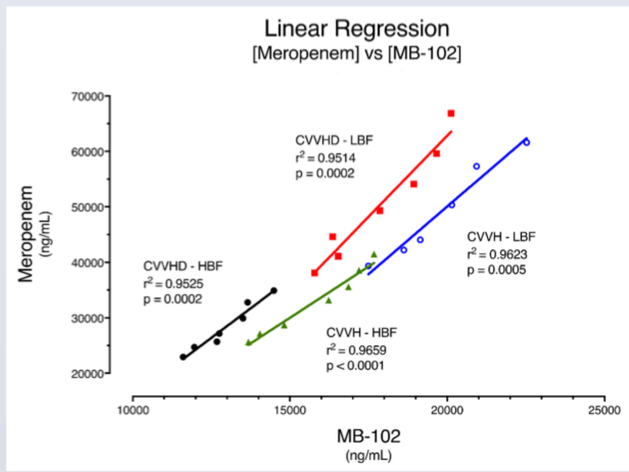


Figure 5: Correlation between the concentration of MB-102 and meropenem for the two CRRT procedures and flow rates employed.

Summary

The time dependence of the transdermal MB-102 fluorescence was highly correlated with the MB-102 plasma pharmacokinetics, as expected. The correlation between MB-102 plasma concentration and meropenem concentration was greater than r^2 ~ 0.95 for all studied CRRT and blood and effluent flow rates.

Conclusion

The feasibility of correlating MB-102 clearance measured using transdermal fluorescence detection with the clearance of an antibiotic such as meropenem is demonstrated in CRRT procedures. Correlations with other medically important antibiotics and other drugs will be the subject of future work.

References

Dorshow, R. B., et al., 2017. Clinical study results of a real-time point-of-care glomerular filtration rate measurement. J Am Soc Nephrol 28, 597.

Bugaj, J. E., and Dorshow, R. B., 2015. Pre-clinical toxicity evaluation of MB-102, a novel fluorescent tracer agent for real-time measurement of glomerular filtration rate. Regul. Toxicol. Pharmacol. 72, 26-38.

Dorshow, R. B., et al., 2015. Initial clinical trial results of a real-time point-of-care glomerular filtration rate measurement utilizing a novel fluorescent tracer agent. J Am Soc Nephrol 26, 259A.