

# MB-102 Clearance During *Ex Vivo* Continuous Renal Replacement Therapy

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## Introduction

- Estimation of glomerular filtration rate (GFR) is widely accepted to assess the kidney's filtering function and determine stages of kidney disease.<sup>1</sup>
- Serum creatinine is commonly measured solute that is used as a clinically acceptable marker in different GFR equations.<sup>2</sup>
- However, creatinine is a poor surrogate because it is insensitive, partially secreted, and time-delayed (kidney injury would not be noted instantly).<sup>3</sup>
- Moreover, serum creatinine concentrations can be affected by multiple factors (age, hydration, muscle mass, diet, etc.) that are not related to renal function.<sup>4</sup>
- MB-102 is a novel fluorescent tracer agent that is exclusively removed from the body by glomerular filtration.<sup>5-6</sup>
- This agent can be detected transdermally to provide the accurate and real-time measurement of renal function.
- MB-102 volume of distribution is similar to iohalamate (~15-20 L)<sup>6</sup>, molecular weight (~372 Da)<sup>5</sup> and plasma protein binding (0%)<sup>7</sup> suggest that it would be removed by renal replacement therapies.

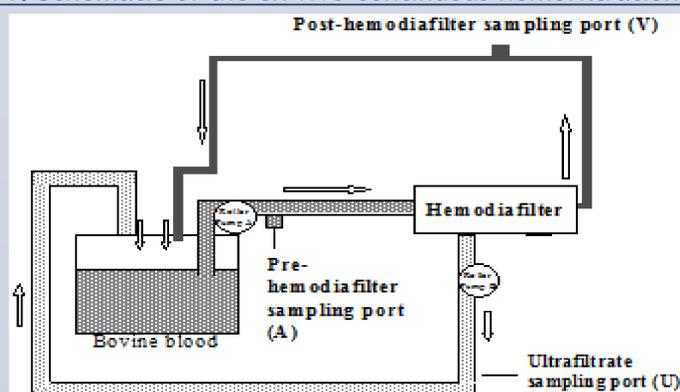
## Objectives

- To determine MB-102 transmembrane clearance ( $CL_{TM}$ ) & membrane adsorption in continuous hemofiltration (CHF) & continuous hemodialysis (CHD).

## Methods

- Validated *ex vivo* CHF and CHD models were performed to assess drug clearances with different combinations of hemofilter types and effluent flows.
- Two commonly-used hemofilters were used in this study:
  - Prismaflex HF1400 hemofilter (polysulfone, Baxter, surface area 1.4 m<sup>2</sup>)
  - Multiflow M150 hemofilter (acrylonitrile, Baxter, surface area 1.5 m<sup>2</sup>)
- MB-102 was added to 1 liter of pH regulated, continuously stirred, maintained at 37°C and citrated-anticoagulated bovine blood to yield final concentrations of ~6.2 mg/L. Urea was added to achieve a BUN ~75 mg/dL as a control solute. Each experiment was repeated 6 times with a new hemofilter and tubing set.
- **Adsorption experiments**<sup>8-11</sup>:  
Adsorption was measured using CHF with a blood flow rate of 200 mL/min and an ultrafiltrate rate of 33 mL/min. Blood samples were collected from the pre-filter port at 0, 5, 10, 20 and 60 min and an ultrafiltrate sample from the ultrafiltrate port at 60 min.
- **CRRT methods**<sup>8-11</sup>:  
CHF was performed with ultrafiltrate rates of 16, 33, 50 mL/min and a blood flow rate of 200 mL/min, while CHD was performed with dialysate rates 16, 33, 50, and 100 mL/min and the same blood flow. Blood and ultrafiltrate/spent dialysate samples were taken from pre- and post-hemofilter and ultrafiltrate/spent dialysate ports after the machine ran for 5 min.
- **Statistical analysis:**  
Student's t-test and analysis of variance (ANOVA) were used to compare differences between the two hemofilters and within each hemofilter type, respectively. Power analysis indicated that six hemofilters were needed to show a 25% difference in clearance between hemofilter types.
- **Assay analysis:**
  - The MB-102 plasma samples were analyzed using a Waters UPLC system with fluorescence detection and external calibration standards.
  - Each sample was diluted 1/100 with 1X PBS prior to analysis.

Figure 1. Schematic of the *ex vivo* continuous hemofiltration system



## Results

- No MB102 adsorption to the CRRT apparatus and either of hemofilters was observed over the one-hour experiment.
- The mean sieving coefficient (SC) from CHF with three different ultrafiltration rates was approximately 1 for both HF1400 and M150 hemodiafilters.
- Urea SC was also approximately 1 at all flow rates with both hemofilters.
- For CHF, hemofilter type and flow rates did not influence MB102  $CL_{TM}$ .
- For CHD, the mean saturation coefficient (SA) was approximately 1 for all dialysate flow rates for HF1400 hemodiafilter.
- However, mean SA reduction was observed from 1 to 0.8 with M150 hemodiafilter at the highest dialysate flow rate of 100 mL/min.

Table 1. Sieving coefficients of MB-102 and urea during CHF experiments

| Ultrafiltrate Flow Rate (mL/min) | MB-102 (n=6) (mean±SD) |           | Urea(n=6) (mean±SD) |           |
|----------------------------------|------------------------|-----------|---------------------|-----------|
|                                  | HF1400                 | M150      | HF1400              | M150      |
| 16                               | 1.14±0.06              | 1.17±0.12 | 1.08±0.03           | 1.00±0.05 |
| 33                               | 1.17±0.03              | 1.17±0.07 | 1.09±0.05           | 1.04±0.1  |
| 50                               | 1.18±0.05              | 1.16±0.07 | 1.08±0.07           | 1.05±0.04 |

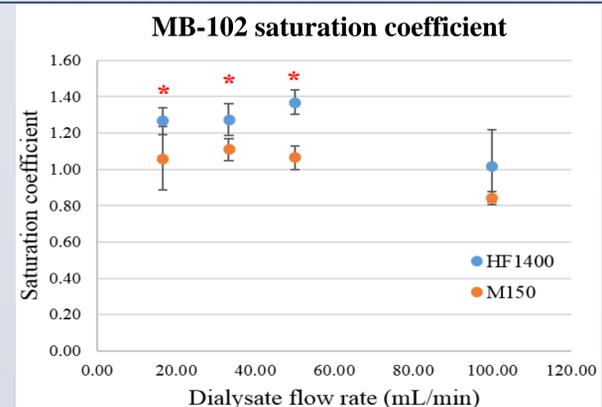
No statistically significant differences occurred between hemofilter types or ultrafiltrate flow rates.

Table 2. Saturation coefficients of MB-102 and urea during CHD experiments

| Dialysate Flow Rate (mL/min) | MB-102 (n=6) (mean±SD) |           | Urea (n=6) (mean±SD) |           |
|------------------------------|------------------------|-----------|----------------------|-----------|
|                              | HF1400                 | M150      | HF1400               | M150      |
| 16                           | 1.27±0.07*             | 1.06±0.17 | 1.04±0.07            | 1.08±0.08 |
| 33                           | 1.27±0.09*             | 1.11±0.06 | 1.19±0.09            | 1.16±0.04 |
| 50                           | 1.37±0.07*             | 1.06±0.06 | 1.17±0.11            | 1.15±0.15 |
| 100                          | 1.02±0.2               | 0.84±0.04 | 1.17±0.19            | 1.35±0.2  |

\*=Represents p-value <0.02 between HF1400 and M150 hemofilters  
Dialysate flow rates that influenced saturation coefficient for both hemofilters (P<0.005).

Figure 2. Mean MB-102 saturation coefficient from continuous hemodialysis



The asterisks indicate statistically significant SA differences between hemodiafilter types during CHD. Additionally, SA at dialysate flow rates of 100 mL/min were significantly lower with both filters than at slower dialysate flow rates. The error bars represent the standard deviation.

## Discussion/Conclusion

- MB-102 is readily removed by CHF and CHD.
- Dialysate and ultrafiltrate flow rates directly influence MB-102  $CL_{TM}$ .
- Hemodiafilter type is not an important determinant of MB-102  $CL_{TM}$  during CH, and only matters in CHD at high dialysate flow rates.
- Transmembrane clearance of MB-102 via CRRT should be accounted when this agent is used for a real-time measurement of GFR in critically ill patients receiving CRRT.

## References

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