Predicting Dose Adjustments in Continuous Renal Replacement Therapy Patients Using an In vitro Continuous Venovenous Hemofiltration Model: A Simulation Study
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Background
Patients in the ICU who develop acute renal failure frequently require continuous renal replacement therapy (CRRT) as artificial support to maintain homeostasis and remove xenobiotics from the body. Continuous venovenous hemofiltration (CVVH) is a form of CRRT that uses the principles of convection to move solute across a filter membrane. During CVVH, drug clearance is dependent on the extracorporeal blood flow, ultrafiltration rate, albumin binding, molecular weight and the volume of distribution of the drug. The use of in vitro modeling to predict in vivo drug clearance during CRRT is representative of translational research that can possibly demonstrate a correlation from bench to bedside. Results generated through in vitro CVVH studies can potentially assist with clinical decisions regarding dose adjustments in the absence of further in vivo studies.

Objectives
This simulation study aims to predict dose adjustments based on the dose normalized AUC of three commonly used antiepileptic medications (levetiracetam, valproic acid, and phenobarbital) in the neuro-ICU using an in vitro continuous venovenous hemofiltration (CVVH) model. The dose normalized AUCs from the in vitro model will be compared to those found in patients with normal renal function in order to determine whether any dose adjustments are necessary.

Methods
Replacement fluid, ultrafiltrate and blood flow rates were based on protocols followed by the University of Maryland Medical Center, Baltimore. Sieving coefficients from previous studies were used to calculate CVVH drug clearance. Simulations were conducted using Phoenix WinNonlin® 6.4 (Pharsight Corporation).

In Vitro CVVH Model Suggests Dose Adjustments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Predicted Dose Adjustment</th>
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</thead>
<tbody>
<tr>
<td>Healthy Patient Dose</td>
<td>CVVH Patient Dose</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000 mg BID</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>100 mg BID</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>1000 mg QD</td>
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</tbody>
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The in vitro CVVH model suggested a dose decrease for levetiracetam and valproic acid, while for phenobarbital, an increase in dose was predicted to match dose normalized AUCs in patient with normal renal function. Dose adjustment predictions were comparable to dosing decisions referred in literature. Data obtained from in vitro CVVH models can potentially help guide drug dosing adjustments without the need to conduct further in vivo studies. Clinicians should monitor the concentrations of the studied drugs in order to maintain adequate safety and efficacy in CVVH patients.

Future Studies
An in vitro model will be developed in order to determine the observed drug clearance of levetiracetam, phenobarbital, and valproic acid. Additionally, a clinical trial evaluating the pharmacokinetics of levetiracetam in patients undergoing CVVH is currently being conducted at the University of Maryland Medical Center. Data gathered from the in vitro study will be compared to the in vivo study to determine whether in vitro models can accurately predict drug clearances and guide dosing adjustments in CVVH patients.

References
5. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Depacon NDA 020593 Clinical pharmacology/Biopharmaceutics review.