Challenges of Drug Dosing During Extracorporeal Membrane Oxygenation

Amy L. Dzierba, Pharm.D., BCPS, FCCM
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Medical Center

Disclosures

• None

Objectives

• Evaluate the use of extracorporeal membrane oxygenation (ECMO) for patients with respiratory failure
• Describe the effects of altered pharmacokinetics and pharmacodynamics of drugs commonly used during ECMO
• Formulate recommendations on dosing strategies based on current literature
What is ECMO?

Blood is drained from venous circulation
Pumped through a membrane
Returned to the patient

ECMO Configurations

Veno-venous (V-V)
Respiratory

Veno-Arterial (VA)
Respiratory and hemodynamic

Respiratory Indications for ECMO

• Severe acute respiratory distress syndrome
  – Bacterial / viral / aspiration pneumonia
  – Shock
  – Trauma
  – Pancreatitis
  – Asthma
• Bridge to lung transplantation
• Asthma
• Pulmonary hypertension
• Pulmonary embolism
ECMO for Severe ARDS

- 90 patients with acute respiratory failure
- Randomized to conventional MV vs. ECMO with MV

Improved Survival Over Time

1971: first adult ECMO for respiratory failure
1979: randomized trial demonstrated no benefit (9.5% survival)
1990-2000: observational studies demonstrated improved survival of 47-66%
2009: H1N1-associated respiratory failure (75% survival)
2011: ELSO registry for H1N1-associated respiratory failure (67% survival)

Advances in Critical Care

- Ventilator management
- Fluid management
- Prevention of infection (CLABsIs, VAPs, CAUTIs)
- Trauma management
- Sedation protocols
- Physical & occupational therapy
Does ECMO Improve Clinical Outcomes in Severe ARDS?

CESAR study
Conventional ventilation or ECMO for Severe Adult Respiratory failure

- Randomized controlled trial
- 180 adults enrolled with severe respiratory failure
- Primary Outcome: survival without severe disability at 6 months
  - ECMO: 57/90 patients (63%)
  - Conventional ventilation: 41/87 patients (47%)

Lancet 2009;374:1351-63

CESAR Trial: Results

- Relative risk reduction in favor of ECMO
  0.69 (0.05–0.97; p = 0.03)

Reasonable Conclusion
Supports a strategy of transferring patients with severe cases of ARDS to a specialized center capable of conducting ECMO as part of a standardized management protocol

Pharmacotherapy for Patients on ECMO
Basic Principles of Drug Elimination

Elimination of drugs depends on:
- Clearance and volume of distribution

<table>
<thead>
<tr>
<th>End Organ</th>
<th>Increased Cardiac Output</th>
<th>Altered Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased Elimination</td>
<td>Increased Elimination</td>
</tr>
<tr>
<td></td>
<td>Increased Plasma</td>
<td>Decreased Plasma</td>
</tr>
<tr>
<td></td>
<td>Concentrations</td>
<td>Concentrations</td>
</tr>
</tbody>
</table>

Drug Alterations in the Critically Ill

<table>
<thead>
<tr>
<th>Organ Dysfunction</th>
<th>Altered PK of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>Increased Protein</td>
</tr>
<tr>
<td></td>
<td>Binding</td>
</tr>
<tr>
<td></td>
<td>Increased Volume</td>
</tr>
<tr>
<td></td>
<td>of Distribution</td>
</tr>
<tr>
<td></td>
<td>1) Circuit Interactions</td>
</tr>
<tr>
<td></td>
<td>2) Increased blood volume</td>
</tr>
</tbody>
</table>

Drug Alterations With ECMO

<table>
<thead>
<tr>
<th>Intensive Care Med 2007;33:1018-1024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion 2005;20:309-15</td>
</tr>
</tbody>
</table>
**Factors Influencing Drug Disposition**

- Volume and type of priming solution
- Site of drug administration
- Membrane oxygenator
- PVC tubing
- Better Bladder®
- Heat exchangers
- Flow rates

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**Predicting Drug Alterations**

<table>
<thead>
<tr>
<th></th>
<th>Hydrophilic Drugs</th>
<th>Lipophilic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General PK</strong></td>
<td>Low Vd</td>
<td>High Vd</td>
</tr>
<tr>
<td></td>
<td>CL dependent on renal function</td>
<td>CL dependent on hepatic function</td>
</tr>
<tr>
<td><strong>ICU PK</strong></td>
<td>Increased Vd</td>
<td>Unchanged Vd</td>
</tr>
<tr>
<td></td>
<td>CL dependent on renal function</td>
<td>CL dependent on renal function</td>
</tr>
<tr>
<td><strong>ECMO PK</strong></td>
<td>Increased Vd (hemodilution)</td>
<td>Increased Vd and CL (circuit-related factors)</td>
</tr>
<tr>
<td></td>
<td>CL unchanged</td>
<td></td>
</tr>
</tbody>
</table>

- B-lactam antibiotics
- Aminoglycosides
- Glycopeptides
- Linezolid
- Morphine
- Fluoroquinolones
- Tigecycline
- Propofol
- Midazolam
- Fentanyl

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**Analgesia and Sedation Management**
Analgesia and Sedation During ECMO

- Patient comfort and ventilatory optimization
- Minimize catheter malposition or dislodgement
- Optimize ECMO flows and decrease oxygen consumption

Analgesic Loss With ECMO

Simulated neonatal ECMO circuit:
- PVC tubing
- Silicone membrane oxygenator

Sedative Loss With ECMO

Simulated neonatal ECMO circuit:
- PVC tubing
- Silicone membrane oxygenator
- Bladder reservoir
- Heat exchanger
Dexmedetomidine Loss With ECMO

Simulated adult ECMO circuit:
- PVC tubing
- Quadrox-D® oxygenator
- Heat exchanger

<table>
<thead>
<tr>
<th>24-hour Dexmedetomidine Loss</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New Circuit</td>
<td>Old Circuit</td>
</tr>
<tr>
<td>Pre-oxygenator</td>
<td>Post-oxygenator</td>
</tr>
<tr>
<td>76-89%</td>
<td>67-93%</td>
</tr>
</tbody>
</table>

Increased Sedation Requirements

Retrospective analysis of 29 patients receiving ECMO
Local protocol = heavy sedation at ECMO initiation

- Daily dose of midazolam increased 18 mg (95%CI 8-29); p=0.001
- Daily dose of morphine increased 29 mg (95%CI 4-53); p=0.02
- No difference in fentanyl daily dose

Patient Experience

40 year old man initiated on ECMO for severe respiratory failure due to pneumonia
Patient Experience

Limitations of Studies

- Simulated circuit does not account for metabolism or elimination of the drugs
- Early circuit studies use neonatal ECMO circuit
- Lack of standardized ECMO configuration
- Variable priming solutions
- Changing blood flow rates
- Unknown implications of aged circuits
- Lack of clinical outcomes associated with observational experiences
- Absence of control subjects

Recommendations: Sedation

- Consider minimal exposure to sedatives
Recommendations: Sedation

• Use continuous infusions for analgesia (fentanyl / hydromorphone) and sedation (midazolam) in patients with severe ARDS at ECMO initiation
• Requirements usually exceed standard doses
• Establish daily sedative goals with potential sedative interruption
• Anticipate significant dose reduction at ECMO discontinuation
• Monitor for signs of delirium / withdrawal

Antimicrobial Dosing

Neonatal Studies With ECMO

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of Distribution</th>
<th>Elimination Half Life</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin1</td>
<td>Increased</td>
<td>Decreased</td>
<td>Extend dosing interval and monitor drug concentrations</td>
</tr>
<tr>
<td>Vancomycin2</td>
<td>Increase to no change</td>
<td>Decreased</td>
<td>Extend dosing interval and monitor drug concentrations</td>
</tr>
<tr>
<td>Cefotaxime3</td>
<td>Increased</td>
<td>No change</td>
<td>Standard dosing regimens</td>
</tr>
</tbody>
</table>

1 Clin Pharmacokinet 2003;42:403-17
2 Pharmacother 1998;18:1082-6
3 Antimicrob Agents Chemother 2010;54:1734-41
Vancomycin With ECMO

- 45 neonates, children, and adults receiving V-V and V-A ECMO
- Results
  - Increased volume of distribution
  - Decreased elimination half-life
- Limitations
  - Fluctuating renal function
  - Variable vancomycin trough goals
  - Older ECMO equipment

Br J Clin Pharmacol 2005;60:265-75

Adult Case Reports With ECMO

<table>
<thead>
<tr>
<th>Drug</th>
<th>Configuration</th>
<th>Drug Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin(^1)</td>
<td>V-V</td>
<td>No effect</td>
</tr>
<tr>
<td>Voriconazole(^1)</td>
<td>V-V</td>
<td>Decreased</td>
</tr>
<tr>
<td>Caspofungin / voriconazole / liposomal amphotericin B(^2)</td>
<td>V-A</td>
<td>Caspofungin and voriconazole levels low to undetectable. No effect on liposomal amphotericin B.</td>
</tr>
<tr>
<td>Tigecycline(^3)</td>
<td>V-V</td>
<td>No effect</td>
</tr>
</tbody>
</table>

\(^1\) J Antimicrob Chemother 2009;63:767-70
\(^2\) Intensive Care Med 2009;35:183-4
\(^3\) J Antimicrob Chemother 2012;67:1047-8

Limitations of Studies

- Very few drugs studied in adult patients
- Simulated circuit does not account for metabolism or elimination of the drugs
- Early circuit studies use neonatal ECMO circuit
- Lack of standardized ECMO configuration
- Variable priming solutions
- Changing blood flow rates
- Unknown implications of aged circuits
- Lack of clinical outcomes associated with observational experiences
- Absence of control subjects
Implications of Inappropriate Antimicrobial Dosing

- Therapeutic failures
- Toxicity
- Development of resistance

Recommendations: Antimicrobials

- Use published PK data in the critically ill to make dosage adjustments
- Therapeutic drug monitoring is critical for dose adjustments
- Monitor the clinical status of the patient

Management of Anticoagulation During ECMO
Effect of ECMO on Coagulation

**Bleeding**
- Clotting Factor Consumption
- Thrombocytopenia

**CLOT FORMATION**
- Activation of Clotting Pathway
- Aggregation / Activation of Platelets

Need for Anticoagulation
- Anticoagulation is necessary to prevent clotting
- An ideal drug would inhibit platelet and coagulation activation without causing bleeding

**Qurox-D® Oxygenator**

Unfractionated Heparin
- Accelerates the action of endogenous antithrombin (AT) and inhibits the formation of clotting factors
- Rapid acting
- Inexpensive
- Reversible
Heparin and Survival

- Retrospective review of 604 pediatric patients on V-A ECMO
- Conducted over a 20 year period
- Indication for ECMO: 75% respiratory, 25% cardiac
- Goal ACT 180-220 sec
- 58% overall survival

Higher doses of heparin (not ACT) was predictive of survival (p<0.0001)

Ann Thorac Surg 2007;83:912-20

Heparin Management

- Loading dose at the time of cannulation
  - 50-100 units/kg
- Maintenance infusion
  - 7.5-10 units/kg/hr
- Depending on bleeding risk at ECMO initiation, heparin may be delayed

Heparin Monitoring

- Activated clotting time (ACT)
- Activated partial thromboplastin time (aPTT):
  - Higher aPTT levels for lower extracorporeal blood flow
  - Lower aPTT levels have been used successfully (40-60 sec)
- Anti-Xa level
- Antithrombin
- Thromboelastogram (TEG)
Direct Thrombin Inhibitors

• Binds to thrombin independently of AT
• Alternative anticoagulant for patients that cannot receive heparin or in the treatment of heparin-induced thrombocytopenia
• Argatroban
  – Use limited to case series and case reports
  – Higher bleeding rates in ICU patients (11%)
• Bivalirudin
  – When compared to heparin, no difference in platelet count or thrombotic complications

Limitations of Current Studies

• Lack of adult studies
• No clear consensus on optimal heparin dose and level of anticoagulation

Recommendations: Anticoagulation

• Anticoagulation should be initiated at the commencement of ECMO to prevent thromboembolic complications
• Heparin remains the primary agent for ECMO anticoagulation
• Maintaining low levels of anticoagulation with routine monitoring reduces the risk of bleeding complications
Summary

- Dose adjustments during adult ECMO are not well defined
- Experience limited to case reports/series
- More thorough pharmacokinetic studies needed with modern technology
- Drug regimens need to be individualized
- Additional extracorporeal devices add to complexity of drug regimens