Pharmacotherapy Management in Patients with Extracorporeal Membrane Oxygenation

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Faculty Disclosure

• I have no conflicts of interest to disclose.
Educational Need/Practice Gap

• Gap = Lack of treatment guidelines and published research often leave providers with no clear way to optimally treat patients

• Need = Our learners need strategies to manage patients on extracorporeal membrane oxygenation (ECMO)
Upon completion of this educational activity, you will be able to:

1. Identify alterations in pharmacokinetics (PK) associated with ECMO

2. Review dose adjustments and monitoring for common medications in critically ill patients on ECMO, including antimicrobials, sedatives, analgesics, and anticoagulation
• What is the desired change/result in practice resulting from this educational intervention?

• As a result of the information/tools provided in this activity, learners should be better able to utilize appropriate pharmacologic therapies to manage patients on ECMO
Pharmacokinetic Alterations

Drug Factors

Disease Factors

Extracorporeal Factors
Critical Illness

Augmented Cardiac Output

Leaky Capillaries/Volume resuscitation

Altered Protein Binding

End-organ Dysfunction

Increased Clearance

Increased Volume of Distribution

Decreased Clearance

Decreased Plasma Concentrations

Increased Plasma Concentrations

Extracorporeal Membrane Oxygenation

- Augmented Cardiac Output
  - Increased Clearance
  - Decreased Plasma Concentrations

- Hemodilution
  - Increased Volume of Distribution
  - Increased Plasma Concentrations

- Drug Sequestration

- End-organ Dysfunction
  - Decreased Clearance
• ECMO Circuit
  • Tubing type
  • Oxygenator membrane
  • Priming solution
  • Age of the circuit
<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Octanol/Water Partition (log p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>95-99%</td>
<td>4.0</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>79-87%</td>
<td>3.9</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>85-91%</td>
<td>3.5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>97%</td>
<td>3.3</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>94%</td>
<td>3.3</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>8-19%</td>
<td>0.9</td>
</tr>
<tr>
<td>Morphine</td>
<td>20-35%</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Drug Factors

Protein Binding

Lipophilicity

Lipophilicity

Nucleic Acids Res. 2008 Jan;36(Database issue):D901-906
Analgesics and Sedatives

Simulated Adult ECMO Circuit

Percentage

0 Minutes

1440 Minutes

Morphine
Midazolam
Fentanyl
Propofol

Lemaitre et al. Critical Care. 2015;19:40
### Analgesics and Sedatives

- Retrospective study of 29 patients on VA or VV ECMO

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Daily Dose</th>
<th>Population Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Increased by 18 mg (95% CI 8-29; p=0.001)</td>
<td>All</td>
</tr>
<tr>
<td>Morphine</td>
<td>Increased by 29 mg (95% CI 4-53; p=0.021)</td>
<td>Conserved renal function</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>No difference (p= 0.94)</td>
<td>Renal dysfunction or renal replacement therapy</td>
</tr>
</tbody>
</table>

Analgesics and Sedation Considerations

- At ECMO initiation, use continuous infusions
- Set daily sedation goals and consider daily interruption of sedative
- After ECMO decannulation, re-evaluate doses of analgesics and sedatives
- Monitor for delirium or signs of withdrawal
Antimicrobial Dosing Considerations

- Therapeutic failure
- Potential emergence of resistant microorganisms
- Toxicity
### β-Lactam Pharmacokinetics in ECMO

- Case control cohort: Total of 41 therapeutic drug monitoring (TDM) results

<table>
<thead>
<tr>
<th></th>
<th>Meropenem (n=27)</th>
<th>Piperacillin/tazobactam (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECMO</td>
<td>Control</td>
</tr>
<tr>
<td>Volume of Distribution (L/kg)</td>
<td>0.46 (0.26–0.92)</td>
<td>0.60 (0.42–0.90)</td>
</tr>
<tr>
<td>Elimination half life (h)</td>
<td>3.0 (2.1–4.8)</td>
<td>2.9 (2.4–3.7)</td>
</tr>
<tr>
<td>Total drug clearance (mL/min)</td>
<td>125 (63–198)</td>
<td>144 (97–218)</td>
</tr>
</tbody>
</table>

β-Lactam Pharmacokinetics in ECMO

# Dose Adjustments for Select Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Log p</th>
<th>Volume of Distribution</th>
<th>Expected Effect</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>85-90%</td>
<td>-0.01</td>
<td>5.78–13.5 L</td>
<td>Moderate sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>50%</td>
<td>-4.4</td>
<td>28–70 L</td>
<td>Minimal sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>24–38%</td>
<td>0.65</td>
<td>88.9 L</td>
<td>Minimal to moderate sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Gentamicin/</td>
<td>&lt; 30%</td>
<td>&lt; 0.0</td>
<td>14–21 L</td>
<td>Minimal sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Tobramycin/Amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>58%</td>
<td>2.56</td>
<td>322 L</td>
<td>Moderate to high sequestration</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Antimicrobial Dosing Considerations

- PK data in adult patients on ECMO are sparse
- Consider loading dose for drugs with moderate to high sequestration
- Dose guided by therapeutic drug monitoring when applicable
- Monitor for signs of infections
• Meta-analysis: 12 studies (1763) patients
  • Any bleeding (33%)
  • Hemolysis (18%)
  • Venous thrombosis (10%)
  • Gastrointestinal bleeding (7%)
  • Disseminated intravascular coagulation (5%)
Hemostasis Alterations During ECMO

1. ECMO Initiation
2. Hemodilution
3. Dilutional Coagulopathy
4. Contact Factor Pathway Activation
5. Thrombin Generation
6. Platelet Activation & Dysfunction
7. Inflammatory Response

Kamdar et al. Semin Perinatol. 2018;42(2):122-128
Coagulation Cascade

Contact activation (intrinsic) pathway

- Damaged surface
- XII → XIIa
- XI → X1a
- IXa

Tissue factor (extrinsic) pathway

- Trauma
- VIIa → VII
- VIIIa

Heparin

Common pathway

- Prothrombin (II)
- Thrombin (IIa)
- Fibrinogen (I)
- Fibrin (Ia)

Cross-linked fibrin clot

- Xa → Va
- X → Xa

Enoxaparin

Bivalirudin

Argatroban

## Anticoagulation Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>• Well known</td>
<td>• Non-linear, variable effect</td>
</tr>
<tr>
<td></td>
<td>• Easy to antagonize (protamine)</td>
<td>• Dependent on AT activity</td>
</tr>
<tr>
<td></td>
<td>• Easy to monitor (aPTT/ACT)</td>
<td>• Possible HIT induction</td>
</tr>
<tr>
<td>Low-molecular weight heparin</td>
<td>• Easy to administer</td>
<td>• Accumulation in renal impairment</td>
</tr>
<tr>
<td></td>
<td>• Lower risk of HIT induction</td>
<td>• Can only be partially antagonized</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>• Independent of AT activity</td>
<td>• Not easy to monitor (anti-Xa levels)</td>
</tr>
<tr>
<td></td>
<td>• Quick onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No HIT induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>Bivalirudin</strong>: cleared renally</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>Argatroban</strong>: cleared hepatically</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guidelines

- Heparin bolus (50-100 units/kg) at time of cannulation, continuous infusion during ECLS
- Monitor ACT, aPTT, or anti-Xa

“These guidelines describe useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care, and are revised at regular intervals as new information, devices, medications, and techniques become available.”
Goals
ACT 180-200 sec
Median antithrombin 70%
Anti-Xa 0.3-0.7 IU/mL

Transfusion Triggers
Platelets <100k
Fibrinogen <145mg/dL

Monitoring Frequency
APTT q6-8h
CBC q6-8h
Fibrinogen >12h
Free hemoglobin >12h
Antithrombin q13-24h
Anti-Xa q13-24h

Practice Survey of 121 ECMO Centers

# Unfractionated Heparin Monitoring

<table>
<thead>
<tr>
<th>Key Factors</th>
<th>ACT</th>
<th>aPTT</th>
<th>Anti-Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Point of care</td>
<td>Central Lab</td>
<td>Central Lab</td>
</tr>
<tr>
<td>Results</td>
<td>Results may be affected (prolonged) by:</td>
<td>Not affected by platelet numbers or function</td>
<td>Least affected by physiologic alterations</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia</td>
<td>Hepatic congestion</td>
<td>Direct assessment of anticoagulant effect of heparin</td>
</tr>
<tr>
<td></td>
<td>• Platelet dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hemodilution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turn around</td>
<td>Rapid (minutes)</td>
<td>Dependent on lab (30 min to hours)</td>
<td>Dependent on lab (30 min to hours)</td>
</tr>
<tr>
<td>Typical goal</td>
<td>160 – 200 for ECMO</td>
<td>1.5 – 3 x baseline (typically 40-70 range)</td>
<td>0.3 – 0.7 IU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.25 – 0.5 IU/mL</td>
</tr>
</tbody>
</table>
Anticoagulation for ECMO at UK HealthCare

• MCS Heparin Protocol
  • Full-Dose ➔ Higher therapeutic targets
  • Low-Dose ➔ Lower therapeutic targets
  • Utilizes both anti-Xa and aPTT concurrently

• ACT protocol

• Fixed dose heparin protocol
Bleeding Complications

• Contributing Factors
  • Systemic anticoagulation
  • Thrombocytopenia
  • Platelet dysfunction
  • Coagulopathy secondary to primary disease and/or liver dysfunction

• Prevention
  • Optimize anticoagulation (avoid over anticoagulation)
  • Maintain platelets
  • Caution with suctioning and placement of lines and catheters
  • Prepare for invasive procedures if necessary
Therapeutic Options

- Administer antidotes/reversal agents when appropriate

- Blood products
  - Red blood cells (RBCs)
  - Platelets Fresh frozen plasma (FFP)
  - Cryoprecipitate

- Pharmacologic agents
  - Local hemostatic agents/sealants
  - Vitamin K
  - Antifibrinolytics
  - Protamine
  - Desmopressin (DDAVP)
  - Recombinant activated factor VII (rFVIIa)
  - Prothrombin Complex Concentrates (PCCs)
Anticoagulation Considerations

- Most data in pediatric population
- Center specific protocols
- Heparin drug of choice for now
- Variable monitoring strategies
- UK primarily uses heparin; aPTT and Anti-Xa
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