Challenges of Drug Dosing with ECMO

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Conflict of Interest

Dr. Turner has no conflicts to disclose

Disclaimer

- Majority of ECMO studies included done in pediatric patients
  - Use of many drugs without FDA pediatric indications
Learning Objectives

• Evaluate the use of extracorporeal membrane oxygenation for patients with respiratory failure
• Describe the role of altered pharmacokinetics and pharmacodynamics from ECMO on drug dosing
• Formulate clinical recommendations based on current literature

ECMO

Extracorporeal membrane oxygenation

Synonyms for ECMO\(^1\):
- ECLA: extracorporeal lung assist
- ECLS: extracorporeal life support
- ECCOR: extracorporeal carbon dioxide removal

ECMO\(^2,3\)

- Extracorporeal Life Support Organization (ELSO) definition:
  - The use of a cardiopulmonary bypass circuit for temporary life support for patients with potentially reversible cardiac and/or respiratory failure
  - ELSO collects data from >115 ECMO centers worldwide through voluntary reporting
  - ECMO first used successfully for neonates with respiratory failure in 1975
ECMO Components

- **Pump**
  - modified roller with inlet pressure control
  - centrifugal or axial rotary pump with inlet pressure control
  - peristaltic pump
- **Membrane Oxygenator**
  - Sweep gas: 100% oxygen or carbogen (5%CO₂, 95%O₂)
- **Tubing**
- Collapsible reservoir/bladder
- Heat exchanger
- Hemofiltration unit for renal dysfunction

Two types of ECMO

- **Veno-Venous (VV):**
  - No hemodynamic support
  - Preferred for respiratory support
    - Avoids using major artery
    - Avoids potential systemic embolism
- **Veno-Arterial (VA):**
  - Required for cardiac support
  - Appropriate for respiratory support
What type of ECMO can be used in a patient requiring respiratory support?

1. VV ECMO
2. VA ECMO
3. Either VV or VA ECMO

SURVIVAL RATES AND INDICATIONS FOR ECMO

ECMO in Neonates

- ELSO survival rates for respiratory failure:
  - 85% ECMO survival and 75% survival to discharge
- Indications:
  - Meconium Aspiration Syndrome (MAS)
  - Congenital diaphragmatic hernia (CDH)
  - Persistent Pulmonary Hypertension of the newborn (PPHN)
  - Respiratory Distress Syndrome
  - Cardiac anomaly
  - Sepsis
  - Pneumonia
ECMO in Pediatrics

- Survival rate on ECMO:
  - ≤ 2 weeks: 61%
  - 2-3 weeks: 53%
  - ≥3 weeks: 38%
- Mortality increases significantly after 2 weeks of mechanical ventilation before ECMO
- Acidosis and receipt of inotropic support while on ECMO independently associated with mortality
- Bleeding and mechanical complications increase duration of ECMO support

ECMO in Pediatrics

- Indications:
  - No specific respiratory indicators
  - Consideration best within first 7 days of mechanical ventilation at high support
  - Cardiac:
    - Early postoperative cardiac failure in the OR
    - In the ICU: pressor and inotrope requirement, metabolic acidosis, decreased urine output for 6 hours
    - Cardiac arrest from any cause
    - Myocardial failure unrelated to operation: myocarditis, myocardiopathy, toxic drug overdose

ECMO in Adults

- Survival rate nearly 50%
- Indications:
  - Respiratory:
    - Acute respiratory failure due to any cause
    - CO₂ retention due to asthma or permissive hypercapnia with PaCO₂>80
    - Severe air leak syndromes
ECMO in Adults 1,8

- Indications:
  - Cardiac:
    - Cardiogenic shock (acute myocardial infarction, myocarditis, peripartum cardiomyopathy, decompensated chronic heart failure, post cardiotomy shock, septic shock in some centers)
    - Bridge to cardiac transplantation
    - Bridge to placement of a ventricular assist device

ANTICOAGULATION WITH ECMO

Heparin 5,9,10

- Primary anticoagulant used in ECMO
  - Bolus (50-100 units/kg) just prior to cannula placement (even if patient bleeding and coagulopathic)
  - Prime (400 units at WCHOB) added to the circuit
  - Continuous infusion (start at 25 units/kg/hr at WCHOB)
- Monitor and adjust infusion based on bedside whole-blood activated clotting times (ACT)
- Target 160 to 200 seconds
- Initially done every 15 minutes
Monitoring effect of heparin \textsuperscript{9,11}

Bedside ACT vs. anti-factor Xa?

<table>
<thead>
<tr>
<th>Bedside ACT</th>
<th>Anti-factor Xa</th>
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<tr>
<td>Done at bedside</td>
<td>Sent to lab: turnaround time &gt;60 minutes, often not run off-hours</td>
</tr>
<tr>
<td>Small amount of blood needed</td>
<td>Requires 2.7mL blood</td>
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Year-long study of 12 neonates on VA ECMO:

\begin{itemize}
  \item No correlation between:
    \begin{itemize}
      \item ACT levels and heparin dose
      \item ACT levels and anti-factor Xa activity
    \end{itemize}
  \item Significant correlation between:
    \begin{itemize}
      \item Anti-factor Xa activity and heparin dose
    \end{itemize}
\end{itemize}

Conclusion:

\begin{itemize}
  \item Anti-factor Xa levels better reflect heparin effect
  \item ACT levels remain best choice for bedside monitoring
  \item Check both anti-factor Xa activity and ACT periodically to assess heparin dosing
\end{itemize}

Action of heparin \textsuperscript{5,10}

- Binds to antithrombin (AT3) - clotting factor
  - If AT3 low, clotting can occur even with large doses heparin
  - Replace AT3 with fresh frozen plasma (FFP) or concentrated AT3 to maintain AT3 in normal range
- Thrombocytopenia
  - Heparin-induced thrombocytopenia (HIT) in ECMO: reported in 10 to 15\% of patients
ALTERNATIVES TO HEPARIN FOR ANTICOAGULATION ON ECMO

Argatroban

- Direct thrombin inhibitor
- Study of 3 sham circuits:
  - One primed with heparin and heparin drip
  - One primed with argatroban and argatroban drip
  - One without prime and argatroban drip
- Results:
  - No clot formation
  - ACTs maintained >1000 s in each circuit
  - Thrombin generation decreased in argatroban circuits versus heparin, despite less prolonged aPTTs
- Authors suggest: argatroban more efficacious than heparin for anticoagulation in ECMO

Argatroban

- Case report of one adult patient with HIT type II on 114 days VV ECMO leading to lung transplant
  - No significant bleeding events
  - Monitored aPTT (target range, 1.5 to 3 times baseline aPTT)
  - Doses ranged from 0.25 to 1.53 mcg/kg/min (just prior to transplant)
- Case series of five patients with HIT on ECMO
  - Monitored ACTs (target 210-230 sec)
  - Doses ranged from 0.2 to 0.35 mcg/kg/min
  - ACTs showed good agreement with aPTT
Argatroban

Study of 9 patients with ARDS
- Monitored aPTTs (target 50-60 s)
- 1st patient got 2 mcg/kg/min (per manufacturer’s recommendation)
  - Resulted in excessive anticoagulation and severe bleeding
- Other patients got 0.2 mcg/kg/min (average maintenance dose 0.15 mcg/kg/min)
  - Recommendation: use a ten-fold lower dose than recommended by manufacturer to achieve appropriate anticoagulation while on ECMO

Bivalirudin

Study of 21 patients (11 adults, 10 children) who underwent postcardiotomy ECMO
- First eight patients: heparin-based anticoagulation
- Last thirteen patients: bivalirudin-based protocol
- Results:
  - Bivalirudin group: longer ACT and aPTT, less blood loss, lower daily cost in pediatric patients
  - Heparin group: more platelet, FFP and AT3 replacement
  - No significant differences in platelet count, antithrombin activity, thromboembolic complications
- Anecdotal use in ECMO with patients with HIT
- Issues: cost, lack of antidote, difficulty monitoring with ACT

Danaparoid

- Case report of one adult with suspected HIT on VA ECMO for 9 days
- Monitored anti-Xa levels only
- Less blood required than in other ECMO reports
- No clotting of circuit or thrombotic complications
- Potential issues with ECMO:
  - Long elimination half-life, no antidote, possibility of cross-reactivity with anti-PF4/heparin antibodies, accumulation in renal failure
Which of the following drugs are possible alternatives to heparin in patients on ECMO:

a. None, heparin use is required
b. Argatroban
c. Bivalirudin
d. Danaparoid
e. b, c, and d

Complications of ECMO

- Bleeding
  - Most serious complication
- Thromboembolism
- Cannula-related complications
  - Decannulation
  - Clotting in the circuit
- Pulmonary embolism or infarction
- Aortic thrombosis
- Coronary or cerebral hypoxemia
- HIT
- Thrombocytopenia
- Infection
- Additional organ failure
  - Renal
  - Hepatobiliary
  - Cardiovascular

Management of bleeding

- Decrease heparin infusion
  - ACT 1.4 to 1.5 times normal
- Transfuse platelets
  - >100,000
- Aminocaproic acid if fibrinolysis suspected
- Aprotinin if platelet dysfunction
- Fresh frozen plasma
- Clotting factor replacement
DOSING CONSIDERATIONS

Considerations for Dosing

- Priming Volume/ hemodilution
- Absorption by circuit
- Recirculation
- Site of administration:
  - Pre-bladder vs. intra-bladder vs. post-bladder
- Non-pulsatile blood flow in VA ECMO

Priming the Circuit

- Volume of circuit depends on circuit type used
  - Increases in total blood volume ranges from 25% (adults) to 125% (neonates)
    - Volumes used in neonatal circuit: 400-500 mL
    - Exceeds blood volume of most full-term neonates
  - Increases effective circulating volume
    - Drugs with large Vd: expect small changes
      - Drug diffuses back to plasma from large tissue reservoirs
    - Drugs with small Vd: expect significant changes
      - The new Vd may alter elimination rate of the drug
Priming the Circuit 5.18-20

- Components:
  - Crystalloid solution (albumin, hetastarch)
  - Packed red blood cells
    - In weights >35kg, can prime without blood
  - Albumin to coat the surface prior to blood prime
    - As little as 0.125g albumin/100mL prime is beneficial
  - Heparin (1 unit per cc prime) when using blood
  - Calcium: replaces the calcium bound by the citrate in banked blood

Absorption to the Circuit 1,6,21,22

- To tubing and/or oxygenator
- Log P (octanol/water partition coefficient)
  - Drugs with high Log P very soluble in organic materials
  - Increased lipophilicity: Expect considerable loss in the ECMO circuit
- May depend on age of the circuit
  - New circuit: significant drug loss
- Difference with type of circuit
  - Centrifugal pump circuits with hollow-fiber membrane oxygenators ➔ less absorption of all drugs

Recirculation 23

- Fraction of oxygenated blood flows back into the circuit instead of the patient’s circulation
- Dependent on circuit pump flow, catheter position, cardiac output and right atrial size
- May alter drug removal
- Less prevalent toward end of ECMO therapy as pump flow rates significantly lower
Site of administration $^{22,24}$

- Pre-bladder vs. intra-bladder administration vs. post-bladder
  - Pre-bladder mimics administration into patients
  - Drug administration post-bladder is optimal, but increased risk of air embolism
  - Many centers administer pre-bladder and let the top of the reservoir act as an air trap

Non-pulsatile blood flow $^{1,23}$

- High flow rates in VA ECMO cause non-pulsatile flow
  - Altered tissue perfusion
  - Reduced capillary circulation
  - Reduced aerobic metabolism
- Kidneys interpret as hypotension
  - Activate renin-angiotensin system
  - Increased extracellular fluid
  - Reduced urine production
  - Impaired sodium extraction

Drugs with high log P have:

- Increased lipophilicity
- Increased water solubility
- High absorption to ECMO circuit
- Low absorption to ECMO circuit
- Both a and c
- Both b and d
Hemofiltration (HF) during ECMO 8,25

- Corrects hypovolemia
- Counteracts systemic inflammatory response (SIRS) by decreasing inflammatory markers
  - ECMO and underlying disease state cause SIRS
- Add HF to the circuit if pharmacologic diuresis is inadequate
  - Set hourly fluid balance goal (100-300 mL/hr in adults)
  - Maintain until normal extracellular fluid volume reached

Study of 61 neonates on ECMO:
- 15 neonates with HF; 46 neonates without HF
- Default filtrate flow rate: 50mL/kg/hr
- Results:
  - Significantly less time on ECMO in HF group
  - Lower fluid balance per day in HF group
  - Fewer blood transfusions in HF group

Pharmacokinetic Changes During ECMO

- Vd
- Clearance
- $T_{1/2}$
- Protein binding
- Renal/Hepatic clearance
- Underlying disease state
- Renal dysfunction
WHAT'S IN THE ECMO LITERATURE?

About dosing changes with ECMO…¹,⁶

- Most case reports done in neonates
- Most studied drugs in ECMO: antibiotics, sedatives, analgesics, anticonvulsants
- Limitations:
  - Few studies
  - Small sample sizes
  - Differences in ECMO technique and equipment
  - Complex patients with varying diagnoses

Drugs noted in ECMO literature

<table>
<thead>
<tr>
<th>Antibiotics:</th>
<th>Vasodilators:</th>
<th>Miscellaneous:</th>
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<tbody>
<tr>
<td>Vancomycin</td>
<td>Hydralazine</td>
<td>Heparin</td>
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<td>Gentamicin</td>
<td>Nesterilide</td>
<td>Oseltamivir</td>
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<td>Tobramycin</td>
<td>Nicardipine</td>
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<td>Amoxicillin</td>
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<td>Insulin</td>
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<td>Cefazolin</td>
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<td>PGE₁</td>
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<td>Antifungals:</td>
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<td>Caspofungin</td>
<td>Benzodiazepines:</td>
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<td>Vorticonazole</td>
<td>Midazolam</td>
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<td>Fluconazole</td>
<td>Lorazepam</td>
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<td>Diazepam</td>
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<td>Opiates:</td>
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<td>Furosemide</td>
<td>Fentanyl</td>
<td>Esmolol</td>
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<td>Bumetanide</td>
<td>Morphine</td>
<td>Amiodarone</td>
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<td>Epinephrine</td>
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<td>Dopamine</td>
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ANTIBIOTICS

Vancomycin 1,19,24,26-28

- Properties:
  - Water soluble
  - Limited plasma protein binding capacity
  - ECMO circuit decreases level of delivery
- Population pharmacokinetic model of 45 patients on ECMO (mainly VV ECMO)
  - Ages: neonates through adults
  - Results:
    - Volume of distribution increased
    - Clearance decreased significantly
    - T_{1/2} prolonged
- Recommendation: use a longer dosing interval

Gentamicin 1,24,28,29

- Properties:
  - Hydrophilic
  - Small volume of distribution
  - ECMO circuit decreases level of delivery
- All studies in neonates
- Results in ECMO:
  - Mean t_{1/2} longer
  - Vd significantly higher
  - Clearance significantly lower
- Recommendation: for neonates without renal impairment
  - Maintenance dose: 2.5mg/kg q18h with follow-up levels
  - 25% lower dose and larger interval
**Tobramycin** 1,24,27,29

- Properties:
  - Hydrophilic: little sequestration by circuit
- Results in ECMO (sheep data):
  - Vd increased significantly
  - Mean t1/2 increased significantly
  - Clearance: no change
- Conclusion: increase dose with no change to interval

**Cefotaxime** 1,30,31

- Ashman et al studied in 2009 and 2010
- Drug clearance estimate similar for ECMO vs. non-ECMO patients
- VD larger for ECMO vs. non-ECMO patients
  - Hemodilution or capillary leakage of protein-bound drug into the extravascular compartment
- Standard dosing yields a sufficiently high $t_{\text{MIC}}$ in ECMO infants
- Conclusion: use standard dosing

**Amoxicillin** 30

- Same researchers as cefotaxime data
- Results:
  - Clearance same as non-ECMO treated neonates
  - Volume of distribution: slightly increased (but few data points)
Ampicillin \textsuperscript{1,32}

- Sequestered by ECMO circuit
  \(\rightarrow\) variable concentrations
- Ex vivo simulation model
  - 24 hours after a single dose, loss due to sequestration in the circuit:
    - Crystalloid-primed circuit: 71.8\% loss
    - Blood-primed circuit: 15.4\% loss

Cefazolin \textsuperscript{1,32}

- Sequestered by ECMO circuit
  \(\rightarrow\) variable concentrations
- Ex vivo simulation model
  - 24 hours after a single dose, loss due to sequestration in the circuit:
    - Crystalloid-primed circuit: no significant loss
    - Blood-primed circuit: 21\% loss

ANTIFUNGALS
Caspofungin 1,21,24

- Report of 2 adult patients on ECMO

- Results:
  - Caspofungin freely water soluble with low log P: sequestration by circuit not expected
  - Peak and Trough levels comparable to healthy volunteers
  - T1/2, clearance and volume of distribution comparable to healthy volunteers
- Conclusion: No dosage adjustment necessary

Voriconazole 1,21,24,32,33

- Sequestered by ECMO circuit leading to variable concentrations
  - Increased drug binding to newer circuit
  - Ex vivo simulation model
    - 24 hours after a single dose, loss due to sequestration in the circuit:
      - Crystalloid-primed circuit: no significant loss
      - Blood-primed circuit: 71% loss

Voriconazole 1,21,24,33

- Report of 2 adult patients on ECMO
- Results:
  - Poorly water-soluble with high log P: partial loss in the circuit expected
  - Authors used a higher initial dose to compensate for expected loss
    - Initially, levels comparable to those in literature
    - Later, levels increased ~60% (more than the larger initial dose)
- Recommendation: monitor plasma levels
Fluconazole

- Prospective study of 10 infants on ECMO
  - Prophylaxis of candidiasis: 25mg/kg once weekly
  - Treatment: 25mg/kg over 2 hr or 12mg/kg over 1 hr

- Results:
  - Higher Vd, similar clearance as non-ECMO historical controls ➔ lower fluconazole exposure
  - Clearance higher with CVVHD
  - Low log P: Minimal extraction by circuit; not affected by age of circuit

- Conclusion:
  - Prophylaxis: dose of 25mg/kg once weekly adequate
  - Treatment: may need higher doses, esp. with CVVHD

Of the three antifungals discussed, which is highly lipophilic thus plasma level monitoring is recommended?

- a. Caspofungin
- b. Voriconazole
- c. Fluconazole

DIURETICS
Furosemide

- One of best studied drugs used in pediatric ECMO
- Sequestration by circuit
  - In vitro analysis found a 63-87% reduction over 4 hours
- Several studies suggest use of continuous infusion preferable over intermittent dosing
  - Wide dosage range reported

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Furosemide

- PK/PD modeling study in 7 neonates
  - Used loading dose to overwhelm effects of sequestration by circuit
  - Results: LD of 1-2mg/kg followed by infusion of 0.2mg/kg/hr yielded urine outputs >6mL/kg/hr with frequent dose reductions
  - Conclusions: Lower loading doses may be necessary in this population
- Study of 31 neonates
  - Results: median continuous infusion of 0.08mg/kg/hour achieved adequate urine output
  - Conclusions: No advantage over intermittent IV dosing

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Bumetanide

- Single-dose PK trial of 11 full-term neonates:
  - Single dose of 0.1mg/kg (recommended 0.015-0.1 mg/kg q6-24hrs)
  - Results:
    - Doubled urine output
    - Remained above baseline for ~3 hours
    - Vd increase
    - T1/2 increase
  - Conclusion: doses at higher end of range dosed less frequently
OPIATES

Fentanyl 1,22,27,28,32,36
- Highly lipophilic (high log P)
  - Significant sequestration by circuit
  - Ex vivo simulation model
    - 24 hours after a single dose, loss due to sequestration in the circuit:
      - Crystalloid-primed circuit: 87% loss
      - Blood-primed circuit: 100% loss
- Higher doses required to achieve desired therapeutic effect

Morphine 1,22,24,27,37
- Lipophilic: Significant sequestration by circuit
  - <40% of dose extracted by circuit/ binding to PVC tubing
  - With older circuit, extraction increases
- Absorbed less than fentanyl
- Long ECMO courses may cause withdrawal after ECMO discontinuation
  - Higher doses of morphine needed after decannulation
Morphine 1,22,24,27,32,37

- Ex vivo simulation model:
  - 24 hours after a single dose, loss due to sequestration in the circuit:
    - Crystalloid-primed circuit: 17.5% loss
    - Blood-primed circuit: no significant loss
  - Preferred opiate for prolonged periods

Which IV opiate is preferred for use in ECMO?

a. Fentanyl  
b. Morphine  
c. Remifentanil  
d. Sufentanil

BENZODIAZEPINES
Midazolam

- Lipophilic: Significant sequestration by circuit
  - >50% sequestered by circuit (60-95% in first hours after cannulation) requiring higher doses
    - Loss higher in new ECMO circuits than used
- Review of 20 neonates on VA ECMO:
  - Doses of 100-300mcg/kg/hr used
  - Results:
    - Increased clearance and volume of distribution
  - Recommended dose per authors:
    - 300 mcg/kg/hour x 6hr then 150 mcg/kg/hour

Midazolam

- Review of continuous midazolam in 20 neonates on ECMO:
  - Group 1 (n=10) continuous midazolam into the circuit, prereservoir
  - Group 2 (n=10) administration via central or peripheral catheter into the patient
  - Results:
    - Significant increase in V_d
    - Venous access administration preferred
    - Plasma t_1/2 substantially prolonged from onset to steady-state
    - Authors’ recommendation: Use higher initial doses

Lorazepam

- Lipophilic: Significant sequestration by circuit
  - <50% of dose extracted by circuit and binding to PVC tubing; as circuit gets older, this number can increase
**Diazepam** \(^{1,21,24,27}\)

- Lipophilic: Significant sequestration by circuit
  - Binds to polyvinylchloride bags

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**Dose interruptions** \(^{39}\)

- Prospective observational study of 20 neonates on ECMO
  - Continuous infusions of morphine and midazolam
  - Infusions stopped 30-60 minutes after cannulation and restarted depending on guidance of frequent pain and sedation scoring
  - Results: Median interruption duration 10:25 hours (2-3 times longer than reported in adults)
  - Authors suggest:
    - Lower cumulative doses may lead to lower incidence of adverse effects and lower doses needed after decannulation

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**ELSO recommendations** \(^{8}\)

- Neonates can be managed on ECMO with a PRN narcotic +/- a benzodiazepine
- Paralysis and high dose continuous narcotic infusions reserved for rare cases
  - Not always followed in clinical practice
STRESS-ULCER PROPHYLAXIS

- Ranitidine 1,24,27,40
  - Vd increased
  - Prolonged elimination
  - No evidence to suggest dosing more than every 12 hours in neonates on ECMO
  - Continuous infusion of 2mg/kg/hour recommended to keep gastric pH >4

- PPIs
  - No information found

ANTI-EPILEPTICS
Phenobarbital 1,24,27

- Sequestration by ECMO circuit
- Case report (1 neonate)
  - Results:
    - Vd slightly larger
    - $t_{1/2}$ unchanged
    - Recommendation: larger load and maintenance doses

Phenytoin and Fosphenytoin 1,24,27

- Sequestration by circuit
- Ex vivo simulation model
  - 24 hours after a single dose, loss due to sequestration in the circuit:
    - Crystalloid-primed circuit: 17.6% loss
    - Blood-primed circuit: 31.4% loss

ANTI-ARRHYTHMIC AGENTS
**Esmolol**

Case report of 1 neonate:
- Patient condition: hypertrophic cardiomyopathy on VA ECMO
- Authors recommended loading dose of 700mcg/kg/min (normal 100-500mcg/kg/min) and maintenance rate of 50-700 mcg/kg/min
- No PK samples done and no info on pharmacologic effect provided
- Suggests: dosing modification may be necessary

**Amiodarone**

- Highly lipophilic: sequestration by circuit likely
- Case report of 4 day old, full-term neonate after tetrology of Fallot repair
- Required 2 additional boluses and dose increase to 20mcg/kg/min
- Amiodarone concentrations measured- within therapeutic range
- Suggests: higher doses needed while on ECMO

**VASODILATORS**
**Hydralazine**

- Study of 23 infants on ECMO
  - Looked at impact of hydralazine on cardiac performance
  - Low dose used (0.15 mg/kg, recommended dose in PICU 0.1-0.6 mg/kg IV q4h)
  - No improvement found in shortening fraction, cardiac output or cerebral blood flow index
  - **Authors’ Recommendation:**
    - Similar dosing as in infants not on ECMO

**Nesiritide**

- Case series of 2 neonates on ECMO
  - Patient condition: 1 with CDH, 1 with hypoplastic left heart syndrome
  - Authors used higher doses to control mean arterial pressure
    - 0.01-0.09 mcg/kg/min
    - Typical doses (non-ECMO): 0.005-0.05 mcg/kg/min
  - Safety of higher doses in infants on ECMO not evaluated

**Nicardipine**

- Quick onset, short t1/2, and readily measured effect (change in BP) ideal for use in patients on ECMO
- Case report of full-term infant with CDH on VA ECMO:
  - Used doses 0.5-1.5 mcg/kg/min, similar to doses in non-ECMO patients
- Case report of 19 month-old s/p hydrocarbon ingestion:
  - Effectively managed initially at 5mcg/kg/min; titrated down to 1-3 mcg/kg/min
  - Suggests: Larger Vd, reduced serum concentration initially
- **Recommendation:** titrate to effect
PULMONARY VASODILATORS

Sildenafil

PK study in 23 infants:
- Temporary increase in clearance and Vd
- Doses of 5-7 mg/kg/day were required to achieve adequate serum concentrations
- Doses needed to be adjusted down to 3-5 mg/kg/day after decannulation
- Both doses used were within the recommended dosage range

INOTROPES
Only reports of Epinephrine and Dopamine use in ECMO 28,32

- Ex vivo study of extraction by circuit following single dose
  - Concentrations measured at 30 min, 3 hours and 24 hours post-administration
  - Blood-primed circuit had minimal impact on serum concentrations of both drugs
    - Crystalloid-primed circuit lead to 96.7% loss of epinephrine after 24 hours
- No in vivo studies found

MISCELLANEOUS

Heparin 32

- Ex vivo simulation model
  - 24 hours after a single dose, loss due to sequestration in the circuit:
    - Crystalloid-primed circuit: 33.3% loss
    - Blood-primed circuit: 53.3% loss
Prostaglandin E₁ (PGE₁) ¹,²⁸

- Case report of 1 neonate
- Patient condition: pulmonary valve stenosis, ductal-dependent pulmonary blood flow and MAS
- Increased Vd due to ECMO circuit prime (~tripled baby’s blood volume)
  - PGE₁: minimal tissue distribution, remains in circulation
  - Decreased pulmonary metabolism
- Dose used: 0.8 mcg/kg/min (usual max of 0.4mcg/kg/min)
- Recommendation: double dose during ECMO

Propofol ¹,²⁴,²⁷

- Significant sequestration by circuit

Oseltamivir ¹,⁴¹

- Case series of 3 children (ages 6, 14, 15) with H1N1
- Initially doubled dose to account for anticipated decreased plasma concentrations on VV ECMO
- Result: Plasma concentrations in 2 patients almost 2-fold higher compared to historical controls
- Conclusion: adequate plasma concentrations can be achieved on ECMO. No changes to standard dosing
Cyclosporine

- Binds to polyvinylchloride bags
- Likely to bind to ECMO circuit

Theophylline

- Review of 75 term neonates and children
  - Continuous infusion aminophylline
  - No loading doses given (except 2 patients)
  - Administration into ECMO circuit prereservoir at rate of 5-15 mcg/kg/min
- Results:
  - Clearance significantly lower in ECMO
  - Volume of distribution higher ECMO
  - Circuit volume expands circulating blood volume
- Authors' conclusion: Use initial loading dose and decreased maintenance infusion rate

Insulin

- Binds to polyvinylchloride bags
- Likely to bind to ECMO circuit
Conclusion

- ECMO can significantly alter drug pharmacokinetics
- Factors such as hemodilution, adsorption to ECMO circuit, recirculation, site of drug instillation into ECMO circuit and non-pulsatile blood flow alter drug delivery
- Altered dosage regimens may be necessary
- More research necessary

References


References


