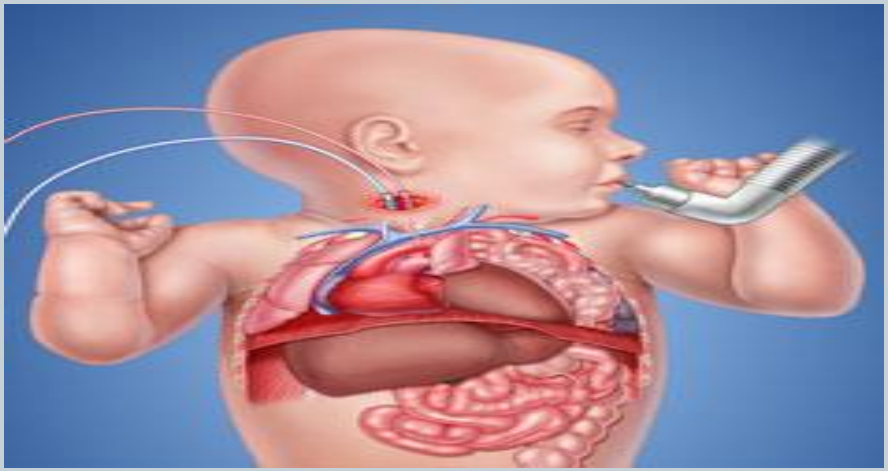
Medications
&
The ECMO Effect



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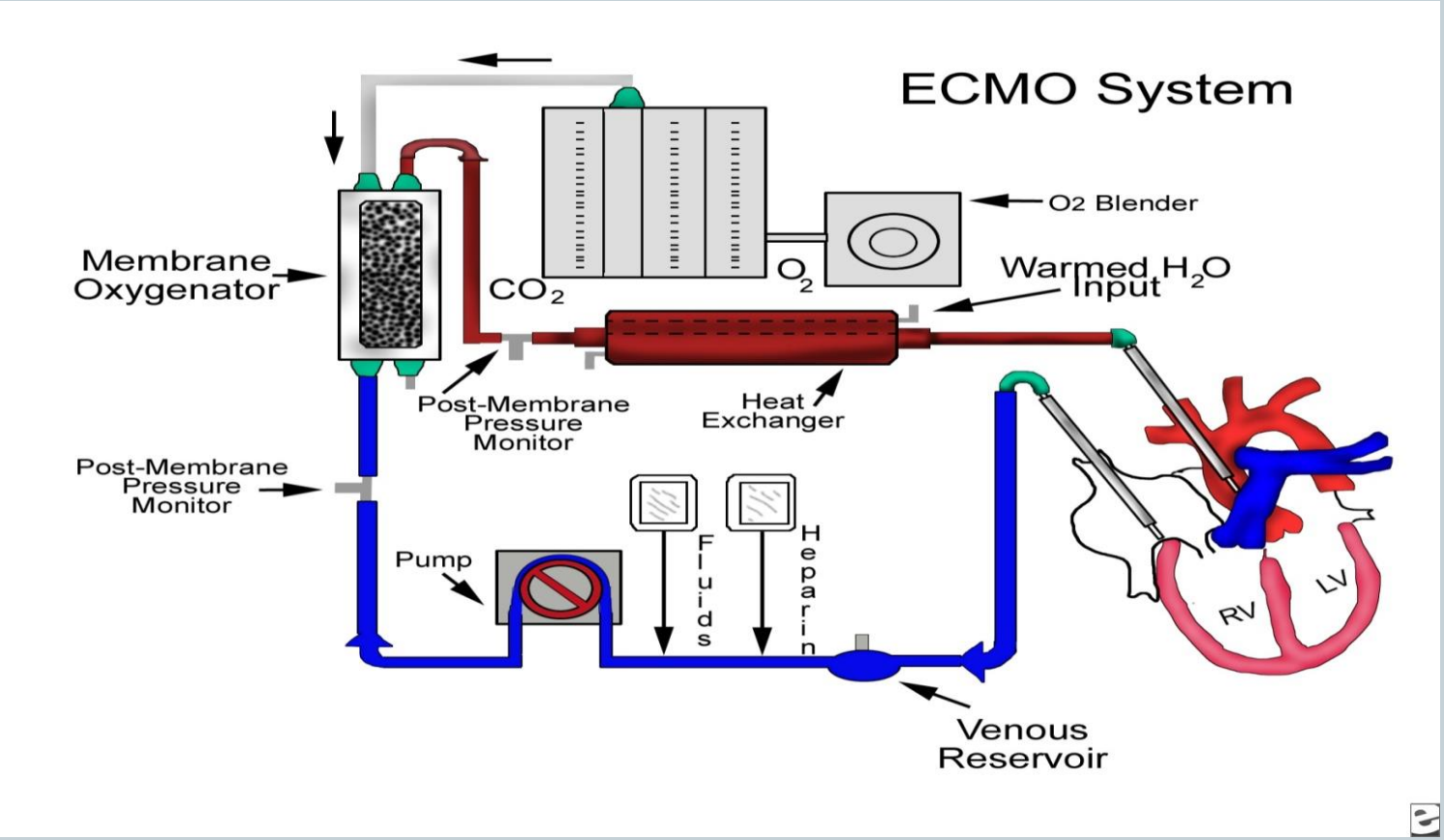
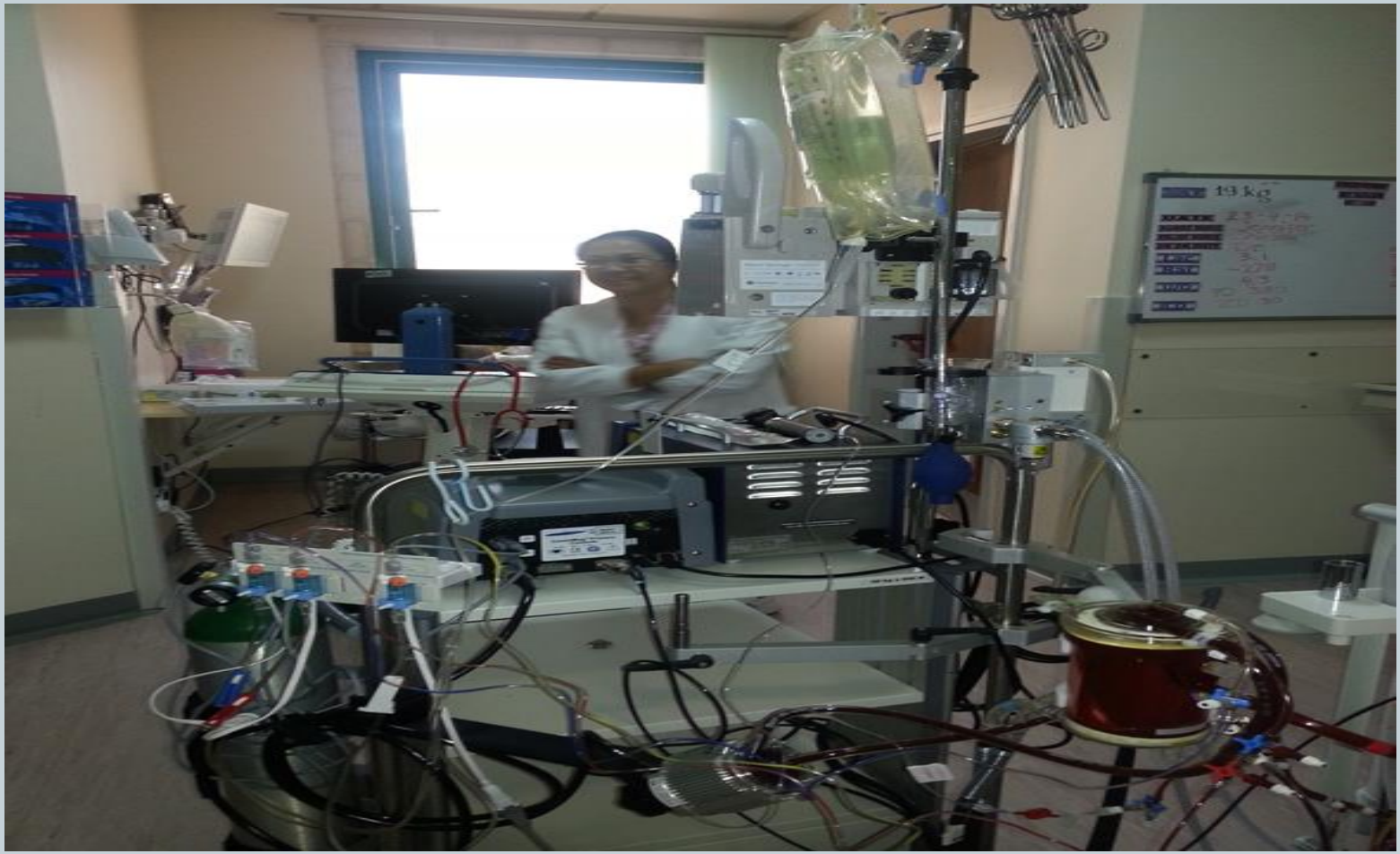
Objectives

- Revise the Principles of ECMO (extracorporeal membranous oxygenation).
- Discuss how ECMO affects the pharmacology of cardiovascular drugs, analgesics, anti-infectives and sedatives.
- Review the current data that addresses the effect of ECMO on commonly used medications in the PICU.



Description of ECMO system [Rodriguez-Cruz, 2011]

SKMC….



- SKMC Experience - ECMO Data till date.
- 72 patients recorded to have gone on ECMO.
- 8 adults and 64 pediatrics.
- 51% of total ECMO patients went onto to be decannulated successfully.

Medications Used in ECMO

- Heparin to prevent clotting of ECMO circuit.
- Inotropes and vasopressors for additional cardiac support.
- Antibiotics for prophylaxis and treatment of infection.
- Electrolyte supplementation.
- Sedatives & analgesics for comfort

Drug choice or dosing in extracorporeal membrane oxygenation

- The studies involving drug administration in ECMO fall into 3 general categories:

World Journal of Critical Care Medicine

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DOI: 10.5492/wjccm.v4.i2.139

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MINIREVIEWS

Designing drug regimens for special intensive care unit populations

Brian L Erstad

Table below lists some of the more important considerations when evaluating published literature and devising dosing regimens in critically ill patients receiving ECMO.

Erstad BL. Designing drug regimens for special ICU populations

Table 10 Drug dosing considerations in adult patients receiving extracorporeal membrane oxygenation

Drug dosing recommendations for an adult on ECMO are unlikely to be evidenced-based
Data from neonatal case reports, case series or studies may not apply to adults
Data from one drug may not be applicable to another even from the same class
Drug regimen recommendations in critical care guidelines may not apply to patients on ECMO
Organ dysfunction apart from the lung and heart complicate interpretation of literature
The contribution of distinct physicochemical properties of drugs to sequestration is unclear
Hydrophilicity or lipophilicity appear to be important factors affecting pharmacokinetics
The therapeutic actions of drugs are not consistently predictable by pharmacokinetics
The design and properties of the equipment change over time with implications for dosing
The priming solution such as blood or blood-derived products may affect dosing

ECMO: Extracorporeal membrane oxygenation.

Pharmacokinetics and Pharmacodynamics

- **Distribution:** the passage of drugs from blood to tissues.
- **Volume of Distribution (Vd) - Key factor in the onset of drug action.**
- This is the apparent volume of body water that drug distributes into to produce a drug concentration equal to that in the blood.
- **Clearance (CL)** – relates the rate of elimination and metabolism to the plasma concentration.
- **Half-life** - completely determined by volume of distribution and clearance.
- **Loading dosage** -If volume of distribution is large, a large loading dose may be needed at the onset of therapy.
- **Maintenance dosage –** more dependent on clearance of the bioavailable drug.
- **Dosage Adjustment** – elimination is altered by disease and ECMO alters PK parameters hence adjustments maybe required.

Pharmacokinetic & dynamic changes during ECMO

- **Increased circulating blood volume**

Increase in Vd –

- ✓ Infant blood volume may more than double in ECMO
- ✓ Exogenous blood to prime the circuit (300-400 mL)
- ✓ Blood transfusions needed to maintain stable hemoglobin levels
- ✓ Demonstrated with drugs such as gentamicin and vancomycin

- **Drug binding interactions with circuit**

Sequestration

- ➢ Highly lipophillic drugs (i.e. fentanyl and midazolam)
- ➢ Easier binding by the polyvinylchloride tubing and oxygenator materials.

- **Clearance (CL) in ECMO**

Decreased in

- ➢ gentamicin, vancomycin and bumetanide
- ➢ **renal** excreted drugs

- **Altered renal, hepatic & cerebral blood flow**

- ➢ Non-pulsatile blood flow
- ➢ Previous injury to organs pre-ECMO

Drug Administration into the ECMO circuit

- Dagan, et al (1993) showed **decreases in serum concentrations** while circulating through the ECMO circuit

% change	Morphine	Phenytoin	Vancomycin	Gentamicin	Phenobarb
New circuit	36%	43%	36%	10%	17%
Used circuit (5 days)	16%	--	11%	0%	6%

The amount of drug lost to the circuit appears to be related to how new the circuit is.

Drug Administration into the ECMO circuit, cont'd

- Mulla et al (2000) showed significant **decreases in serum concentrations** due to uptake by the PVC tubing of ECMO circuit

% Decrease	Midazolam	Lorazepam	Diazepam	Propofol
No albumin	68%	40%	88%	98%
Albumin	76%	52%	96%	99%

When albumin was used to prime the circuit, they found an additional 10% increase in uptake of the sedatives.

SKMC practice = Saline for adults; blood for pediatrics.

Drug Administration into the ECMO circuit, cont' d

- Green, et al (1990) showed the **clearance rate of heparin doubled** while on ECMO compared to when decannulated
  - 3.8 mL/kg/min vs 1.6 mL/kg/min
  - Nearly 50% of the heparin dose was lost in the circuit.

Anticipate higher dosing in ECMO since nearly 50% of the heparin dose was lost in the circuit.

Analgesics

- **Fentanyl – Sequestration**
  - Up to **70% of the dose has been sequestered** by the silicone membrane oxygenator.
    - Saturation kinetics – once the binding sites are saturated, less drug is needed to maintain sedation.

- **Morphine – Sequestration and Clearance**

  Dagan et al (1994) showed a ***decrease* in clearance** of morphine while on ECMO
  - 34 mL/kg/min vs 63 mL/kg/min
  - Authors postulated this may be an effect of decreased hepatic blood flow.
  - However morphine clearance in general is variable and the range of CL values in newer studies exceed those which were published previously for infants who were receiving morphine.
  - **This suggests that morphine therapy should be subsequently guided by clinical monitoring.**

Antibiotics

Journal List › Crit Care › v.19(1); 2015 › PMC4476232

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Meropenem therapy in extracorporeal membrane oxygenation patients: an ongoing pharmacokinetic challenge

Patrick M. Honore,✉ Rita Jacobs, Inne Hendrickx, Elisabeth De Waele, Viola Van Gorp, and Herbert D. Spapen

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Antibiotics

- **Meropenem – Stability & Sequestration**

  - needs plasma levels above (MIC)the minimum inhibitory concentration of the pathogen for 40 % of the dosing interval.
  - Many patients with severe sepsis do not attain this PK target, with recommended meropenem doses .
  - Thermolabile - degraded and significantly sequestered in (ECMO) circuit after 4 to 6 h of treatment.

- **Vancomycin – Sequestration, TDM**

Shekar et al *Critical Care* 2012, **16**:R194

  - hydrophilic drug
  - **no significant loss**
  - differences in methods and populations
  - recommendation of a dosing adjustment is not possible
  - Be guided by therapeutic drug monitoring.

Antibiotics

- Optimization of meropenem treatment during ECMO requires **either**

more frequent dosing

dose increase

prolonged infusion

- Ideally, meropenem should be infused continuously over 24 h but, due to its relative instability at room temperature, only a 3-hour infusion is safely feasible.

We have adopted the prolonged 3-hour infusion of meropenem in our SKMC sepsis ordersets.

- Future adaptations must be anticipated.

Antibiotics

Cefotaxime (CTX)

- The **standard cefotaxime** dose regimen provides sufficiently high concentrations in ECMO infants.
- The CTX Vd is higher in ECMO patients than in non-ECMO patients (1.82 versus 0.68 to 1.14 liters).
- CTX clearances are similar.
- **Gentamicin**
  - Cohen (1990) & Batt-Mehta (1992) both showed an **increase in Vd** (0.51-0.67 L/kg) along with **increase in half-life** (5.7-10 hrs) **lower clearance** in ECMO patients.
  - To achieve therapeutic levels, **extension of interval** was recommended in neonates without renal impairment.
  - Dose: 2.5-3.5 mg/kg IV q18-24h

Pharmacokinetics of Cefotaxime and Desacetylcefotaxime in Infants during Extracorporeal Membrane Oxygenation Maurice J. Ahsman, 2010

Anti-arrhythmic Agents

- Experience with this drug class in children on ECMO has been reported for only two antiarrhythmic drugs.

Esmolol

- extremely short acting β1-selective β-blocker
- **loading dose of 500mcg/kg followed by 25–200mcg/kg/min that can be titrated to effect.**
- The maximum reported dose was 1000 mcg/kg/min .
- There is one case report of esmolol use in a newborn infant with hypertrophic cardiomyopathy on venoarterial ECMO.
- **The patient was loaded with 700 mcg/kg and an infusion started at 50 mcg/kg/min and titrated up to a maximum of 700 mcg/kg/min.**
- **No adverse events were noted, and the infant was able to be decannulated from ECMO 24h after initiation of the esmolol infusion.**
- However, no information regarding pharmacologic effect was provided and no PK samples were collected.

Anti-arrhythmic Agents

Amiodarone – Dosing Reqiurement

- **loading dose of 5mg/kg followed by an intravenous infusion of 5–15mcg/kg/min.**
- However, infusion rates as high as 25mcg/kg/min have been tolerated in infants postoperatively.

case report

- 4day old, full term infant who developed JET following tetralogy of Fallot repair.
- The patient was loaded with amiodarone 2.5mg/kg and started on an infusion of 10mcg/kg/min
- required ECMO 5 hours post-operatively for persistent JET-associated hypotension.
- **required two additional boluses of amiodarone**
- **increase in the infusion rate to 20mcg/kg/min.**
- Amiodarone concentrations measured during this period were **within the therapeutic range** (0.9mg/L and 2mg/L on days 2 and 4, respectively).

- **In this case, higher amiodarone doses were required to reach therapeutic concentrations in a patient on ECMO.**

Inotropes

Epinephrine and Dopamine - Sequestration

- Numerous inotropic and vasopressor drugs are used in children on ECMO, but only epinephrine and dopamine have been studied in this patient population.

Report

- An *ex **vivo*** **study** evaluated the **extraction of dopamine and epinephrine** by the ECMO circuit after administration of a single dose of dopamine (5 mg) and epinephrine (0.5 mg).
- measured epinephrine and dopamine concentrations at 30 min, 3h, and 24h post administration.
- calculated the extraction efficiency of the isolated ECMO circuit primed with blood.
- **It was found that the circuit by itself minimally impacts the serum concentration of these two drugs.**

Diuretics

Furosemide

- Furosemide is a loop diuretic and one of the best studied medications in children supported with ECMO.
- Dosing can be intermittent (0.5–2mg/kg IV up to every 6h) or continuous (**max 0.4mg mg/kg/hr).**
- PK modeling found that a loading dose of 1 mg/kg followed by an infusion of **0.2 mg/kg/hr resulted in urine output in excess of 6 ml/kg/hr.**
- **This suggests that a lower furosemide dose may be required in this population supported by ECMO, however, due to the wide variability in urine output reported (0.8–8.4 ml/kg/hr) the most appropriate furosemide dose remains to be determined.**
- While this was a well-designed study, it was limited by small sample size (n=7) and larger PK/PD studies would be helpful to determine optimal dosing of this drug.

Pulmonary vasodilators

Sildenafil

- Pulmonary hypertension is a common indication for ECMO in infants.
- Sildenafil is a potent phosphodiesterase (PDE-5) inhibitor dosed in infants and children at **2–8 mg/kg/day orally divided into four doses**.
- A PK study of sildenafil in 23 infants (mean gestational age 38 weeks with a mean post natal age of 9.6 days) supported by **ECMO.**
- **Doses of 5–7mg/kg/day were required** to achieve adequate serum concentrations.
- **Dosing adjustments down to 3–5 mg/kg/day were needed after decannulation.**
- **When sildenafil is started in children supported by ECMO, the dose should be decreased after decannulation from ECMO**.

Other

Prostaglandin – Volume of Distribution

- Prostaglandin E1 (PGE1) - maintain the patency of the patent ductus arteriosus in ductal-dependent congenital heart lesions prior to surgical repair.
- Investigationaly used for treatment of pulmonary hypertension in infants.

Case report

- Infant with pulmonary valve stenosis
- PGE1 doses of **0.8 mcg/kg/min** **(normal range 0.01–0.1mcg/kg/min, max 0.4 mcg/kg/min)** were required to maintain ductal patency.
- **Exogenous blood needed to prime the ECMO circuit substantially alters the Vd and hence higher PGE1 doses were required.**

ELSO general guidelines 2015

- **Heparin (UFH):** bolus 50-100 unit/Kg cannulation continuous infusion (no standard dose; 20-70 u/Kg/h)
- **ACT:** measured hourly (more if needed)
  ACT: 1.5 times normal level
- **PTT:** less reliable than ACT (?)
  No target given (1.5 times baseline)
- **Other measure:** heparin concentration or TEG used in some centers

Extracorporeal Life Support Organization (ELSO)

- **Platelets :** over 80 000 / µL
- **Fibrinogen level:** daily measure keep in normal range (2.5-3 g/dL)
- **Surface coating:** «coated circuit may be useful»
- **Antithrombin:** level maintained between 80-120%. If clotting occurs, and AT level not available, give AT concentrate or FFP
- **Bleeding:** returning coagulation to normal status consider antifibrinolytic drugs site specific actions (ex: cannula) prevention: best treatment!

PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 19 Number 2 February 2013

Antithrombin Administration during Pediatric Extracorporeal Membrane Oxygenation

ATIII

- Based on 4 studies (no RCTs) and 3 abstracts
- Could reduce the dose of heparin required
- Could produce a more consistent anticoagulation
- Frequency of supplementation and dose not defined
- Risk of bleeding if acute correction
- Appeared safe in pediatric patients (Artificial Organs 2011; 35: 1024-8)

O ptim … vels of
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variation among programs in both therapies and monitoring.[3] This variation is based not only on differences in clinical experience but also on the continued integration of technologic improvements in circuit components as well as

monitoring.[7] They reported a mean antithrombin level of only 45±15% in the 14 infants, with an average of 71±17% in the four children over 1 years of age. Similar results were reported by Bembea and colleagues in the January 2013 issue

Heparin Induced Thrombocytopenia (HIT)

- In critically ill patients on ECMO who were receiving Argatroban for suspected heparin-induced thrombocytopenia,

- **Argatroban** requirements based on activated partial thromboplastin time monitoring were found **10-fold lower** than the 2 µg/kg per minute dose recommended in product labeling. (Beiderlinden, 2007)

Ranucci *et al. Critical Care* 2011, **15**:R275
http://ccforum.com/content/15/6/R275

CRITICAL CARE

RESEARCH Open Access

Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation

Marco Ranucci[1*], Andrea Ballotta[1], Hassan Kandil[1], Giuseppe Isgrò[1], Concetta Carlucci[1], Ekaterina Baryshnikova[1] and Valeria Pistuddi[1], for the Surgical and Clinical Outcome Research Group

"Conclusion:
Bivalirudin as the sole anticoagulant can be safely used for postcardiotomy ECMO, with a better coagulation profile, less bleeding, and allogeneic transfusions.

No safety issues were raised by this study, and costs are reduced in bivalirudin-treated patients" **?**

But caveats:

- Alternative in HIT but wont help in Heparin coated circuits.
- Acquisition cost considerably higher.
- lack of antidote.

Key Messages

- Sequestration of drugs in the circuit may have implications on both the choice and dosing of a particular drug prescribed during ECMO.
- Lipophilic drugs appear to be more significantly sequestered in the ECMO circuit.
- Fentanyl and midazolam are more significantly sequestered than morphine.
- Meropenem may have to be administered more frequently or by a continuous infusion during ECMO.

Key Messages

- Higher amiodarone doses were required to reach therapeutic concentrations in a patient on ECMO.
- The circuit by itself minimally impacts the serum concentration of these Epinepherine and Dopamine.
- Heparin (with ATIII): cornestone of anticoagulation during ECMO.
- Due to lack of studies, it is unknown what pharmacokinetic changes occur with other medications used to support the patient on ECMO.

Recommendations

- Paucity of literature - precludes any meaningful evidence-based recommendations.
- **Extrapolate information** from the limited pharmacokinetic studies that have been conducted drugs in ECMO technologies in recent years that may influence previous study findings.
- For **drugs titrated to clinical effect** such as opioids, the clinician may either choose to use less lipophilic agents such as morphine (assuming no renal failure) or use more lipophilic agents like fentanyl with the appreciation that higher than expected doses may be needed.
- For some drugs, **therapeutic drug monitoring** may be available and useful.
- For lipophilic or thermolabile (*e.g.*, carbapenems and ampicillin) drugs that are not titrated to clinical effect and for which therapeutic drug monitoring is usually not available, the clinician must be alert for potential **therapeutic unresponsiveness** or failure due to inadequate dosing.

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