Managing Delirium in a patient with Extracorporeal Membrane Oxygenation (ECMO) machine as bridge to lung transplant:
A Case report

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Introduction

Due to COVID pandemic, there have been increased needs for ECMO circuits to support patients with respiratory failure. Unfortunately, due to pharmacokinetics (PK) alterations of commonly used sedative and psychotropic medications by the ECMO circuits via sequestration and increased volume of distribution (V_d), new sedation approaches are required to manage delirium and agitation. This is especially important given psychomotor agitation while on ECMO support can result in adverse clinical outcomes such as decannulation of circuits, thrombosis and thromboembolism. We present a case of COVID pneumonia patient on ECMO support, whose delirium symptoms were managed with a novel psychopharmacotherapy protocol.

Case Description

57 y/o Hispanic male patient with no past psychiatric history, past medical history of obesity, preDM, HTN, OSA on CPAP admitted to outside hospital on 11/30/21 due to hypoxic respiratory failure secondary to COVID pneumonia. Patient received remdesivir and dexamethasone course, transferred to Stanford Hospital on 12/20/21 for higher level of care. On admission, patient required to be on HFNC FiO2 to 90%. On 12/23/21 in setting of worsening hypoxic respiratory failure, patient required to be intubated and by 1/7/21 due to worsening acute respiratory distress syndrome (ARDS) and clinical deterioration, patient placed on venovenous (VV) ECMO with bridge to bilateral lung transplant. Psychiatry consulted on 1/11/21. Below, we will list psychotropic medication management/changes and corresponding RASS (Richmond Agitation Sedation Scale) per week. Bolded changes show important clinical implications.

Rx (Brand)	Mechanism of Action	Peak Plasma Time	Bioavailability	T½	Metabolism	Excretion	Deliriogenic	Log *P* value / PB(%)	Hydro ↓ vs Lipophylic ↑	Re ECMO % Sequestration
Guanfacine (Tenex)	α-2 agonist	1 – 4 hrs	80%	17 hrs	CYP3A4	R-↓	↔	**0.86** / 70	↑	*<not studied>*
Dexmedetomidine (Precedex)	α-2 agonist	46 min	65%	2 hrs	H.Gluc / CYP2A6	R-↓	↔	**2.8** / 94	↑↑	**40–64%** sequestration decline throughout Tx
Propofol (Diprivan) – "milk of amnesia"	$Gaba_A$ agonist, ↓ rate of dissociation from GABA-r; Na+ChBlk; NMDA antagonist; ago-endocannabinoid system	40 min	37%	40 min	Hepatic oxidation and conjugation to sulfate and glucuronide conjugates	R-↓	↑	**3.79** / 95-99	↑↑↑	**70–98%** Propofol Infusion Syndrome
Midazolam (Versed)	$Gaba_A$ agonist	30 min	87%	1.5 – 2.5 hrs	H.Oxy / CYP3A4 (↑PI)	R-↑	↑↑↑	**4.33** / 97	↑↑↑	**68–89%**
Phenobarbital	(GABA)-A receptor agonist; inhibition GLU-induced depolarization.	1 – 2 hrs	90%	53 – 118 hrs	CYP450 and UGT mediated	25–50% R	↑↑	**1.47** / 45-70	↑	***< 40% Tx Level: 10-40 mcg/mL***
Morphine (Roxanol) – ER/SOL/IV	μ, k & δ-Opioid agonist	20 min	80 – 100%	3-7 hrs	H.Gluc, morph-6-glucuronide (20X morphine)	R (12%) F (10%)	↑↑	**0.9** / 35	↑	**4–40%** histamine release →bronchospasm & hypotension
Hydromorphone (Dilaudid) – PO/SOL/IV	μ, k & δ-Opioid agonist, 11X more potent than morphine	15 – 30 min	62%	1.5-3.5 hrs	CYP2D6	R-↑	↑↑	**0.89** / 19	↑	*<not studied>* expected to be low; no active metabolites
Ketamine (Ketalar)	noncompetitive antagonist NMDA & AMPA R; at ↑ muscarinic cholinergic and monoaminergic receptors, Ca+gated ion channels and μ-, σ-, κ-, and δ-opioid receptors	5 – 30 min	93 – 100%	2-3 hrs	N-demethylation→ AM → H.Gluc.→ IM	R (91%) F (3%)	↑↑↑	2.9 / 47	↑↑	*<not extensively studied>* Little sequestration described // documented emergence delirium
VPA (Depakene, Depakote) – IR/ER/SOL/IV	NMDA antagonist; blocking voltage-gated NA+, K+,& CA+ channels, inhibit GAD; GABA potentiation	1–5 hrs	89%	9-16 hrs	CYP2C9, 2C19, 2A6, UGT-glucuronidation	R-↓	↔	**2.75** / 80-90	↑↑	*<not studied>*
Gabapentin (Neurontin) – PO/SOL	inhibition α2δ-1&2 subunit voltage-gated CA+ channels	3 hrs	60 – 27% Inversely proportion to dose	5-7 hrs	∅	R-↓	↔	**-1.1** / <1	↓	*<not studied>*
Pregabalin (lyrica) – IR/ER/SOL	inhibition α2δ-1&2 subunit voltage-gated CA+ channels	1 hrs	>90%	6.3 hrs	∅	R (90%)↓	↔	**-1.78** / <2	↓	*<not studied>*
Haloperidol (Haldol) – PO / IM/ IV /LAI	DA-2 antagonist	10-20 min / 30–60 min	60–70%	21–24 hrs	CYP2D6 & ↓ CYP3A4	F (15%)-↓ R (40%)-↓	↔	**4.3** / 7-11	↑	*<not studied>*
Quetiapine (Seroquel) – IR/ER	5-HT 1A and 5-HT2 antagonist; D1 & D2 antagonist; α1,α2, H1 antagonist	1.5 Hrs (6hrs ER)	100%	6-7 hrs	CYP3A4	R (73%)-↓ F (20%)-↓	↔	**2.8** / 83	↑↑	*<not studied>*

Case Description cont.

1/11/21 – 1/16/21
- RASS -3 to +3
- Drips
  - Dexmedetomidine 1.2 mcg/kg/hr,
  - Hydromorphone 2mg/hr
  - Midazolam 2mg/hr
- Psychotropic medication changes
  - Haldol 2mg IV BID, Haldol 3mg IV QHS
  - Gabapentin 900mg PO TID
  - Guanfacine 1mg PO BID 1.5 mg PO QHS
  - Suvorexant 10mg po qhs
  - Hydroxyzine 50mg

1/17/21 – 1/23/21
- RASS -3 to +3
- Drips
  - Dexmedetomidine 1.2 mcg/kg/hr
  - Hydromorphone 3mg/hr
  - Midazolam 2mg/hr
  - Ketamine 20mg/hr
  - Propofol pushes
- Psychotropic medication changes
  - Haloperidol → aripiprazole due to ↑ QTC
  - VPA was added

1/24/21 – 1/30/21
- RASS -3 to **+2**
- Drips
  - ↑**Dexmedetomidine** 1.6 mcg/kg/hr
  - Ketamine 30mg/hr
  - Hydromorphone 2mg/hr
  - Propofol 15-40mcg/kg/min
- Psychotropic medication changes
- ↑VPA dosage 1750 mg PO
- **Pt improved – started working with PT and OT on 1/28/21**

1/31/21 – 2/6/21
- RASS: -3 to +3
- Drips
  - ↑ **Dexmedetomidine**: 2.0 mcg/kg/hr
  - Ketamine 50mg/hr
  - Hydromorphone 5mg/hr
  - Propofol 15mcg/kg/min
  - Midazolam 3mg/hr
- Psychotropic medication changes
  - Discontinued Gabapentin
  - **Started Pregabalin 200mg po q6h**
- **Patient listed for transplant**

2/7/21 – 2/13/21
- RASS: -2 to +2
- Drips
  - **Dexmedetomidine 2.0 - 2.5 mcg/kg/h**
  - Propofol 25-40mcg/kg/min
  - Hydromorphone: 1-3 mg/hr
- Psychotropic medication changes
  - Aripiprazole was discontinued due to high sequestration
  - Valproic Acid increased to 3000mg PO total daily dose; Trough Level: 35.1

2/14/21 – 2/20/21
- RASS: -3 to +3
- Drips
  - Dexmedetomidine 2.0 - 2.5 mcg/kg/h
  - **Propofol 25-40mcg/kg/min → OFF**
  - Hydromorphone 1-3 mg/hr
- Psychotropic medication changes
  - **Phenobarbital started 15mg po TID**
  - **Subsequently propofol was weaned off**
  - VPA weaned off due to hyperammonemia
  - Discontinued all neuroleptics due to ↑QTC

2/21/21 – 2/24/21
- RASS: -2 to +2
- Drips:
  - DEX 2.0,
  - Hydromorphone 2 mg/hr,
  - propofol **OFF**
- Psychotropic medication changes
  - **Increased phenobarbital 25mg q6h**
  - **Lung transplant 2/24/21**

Discussion

With no clear guidelines on managing sedation/delirium in patients with ECMO support at this time we propose following novel protocol that utilizes drugs with lowest lipophilicity and protein binding potential of its class (summarized in table 1). 1) Dexmedetomidine – alpha 2 agonists has favorable clinical use profile than other sedative drips. Though institutionally, maximum rate celling was set at 1.2 mcg/kg/hr, we were able to raise the rate to 2.5 mcg/kr/hr without any significant cardiac / pulmonary side effect, while having clinical benefits of managing agitation.

2) Gabapentinoids –Gabapentinoids are calcium channel modulators which lowers neuronal excitability and they have low lipophilicity and low protein binding property. We specifically chose pregabalin, given its favorable pharmacokinetics over gabapentin such as faster rate of absorption and increased bioavailability especially at higher doses.

3) Phenobarbital - Phenobarbital not only allosterically modulate GABA-A receptor, it also inhibits NMDA receptors, thus addressing hyperglutaminergic state in delirious patients. In our case, with addition of phenobarbital, propofol was able to be weaned off, while patient remained in behavioral control, participate in PT/OT and successfully receive lung transplant.

4) Opioids - Patient's with ARDS, who are intubated, and on ECMO support can benefit from judicious use of opioids by managing underlying pain and air hunger. Out of the opioids, we found morphine to have most favorable pharmacokinetic profile.

Conclusion

ECMO circuit adds extra layer of complexity for management of delirium due to significant changes of PK. Though we have identified medications that has least PK changes from ECMO, more longer term studies that addresses fundamental problems of sequestration and increased V_d are needed.

Reference

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