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Role of Methadone in Extracorporeal Membrane Oxygenation: Two Case Reports

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Abstract: Extracorporeal membrane oxygenation (ECMO) affects pharmacokinetics/dynamics of drugs in unpredictable ways. Anecdotally, ECMO patients require high doses of opioids and sedatives, leading to concerns of tolerance. Methadone is a long-acting synthetic opioid with antagonist properties at the n-methyl-d-aspartate (NMDA) receptor. It has been shown to improve spontaneous breathing trials and weaning from mechanical ventilation; however, there is no literature describing its use in ECMO. We describe two patients from the cardiac surgery intensive care unit at Cedars Sinai (Los Angeles, CA) on ECMO for over 30 days maintained on methadone. **Keywords:** extracorporeal membrane oxygenation, methadone, analgesics, sedation, critical care. *J Extra Corpor Technol. 2018;50:252–5*

Combining the decreased mortality rates demonstrated in the CESAR trial (1) (conventional ventilatory support vs. extracorporeal membrane oxygenation for severe adult acute respiratory failure) and H1N1-related acute respiratory distress syndrome (ARDS) in 2009, VV ECMO (veno-venous extracorporeal membrane oxygenation) has gained widespread acceptance as the most intensive form of pulmonary support used for patients with refractory acute respiratory failure (2). Despite increases in ECMO use, optimal sedation strategies (when needed) are not known.

Although the goals of sedation in both ECMO and non-ECMO patients are similar, there are specific nuances in drug metabolism during ECMO therapy that are important to consider (3). Shekar et al. (4) describe increased volume of distribution, decreased clearance/absorption, active metabolites, lipophilic properties, instability at physiological temperatures, and sequestration within the circuit as variables leading to unpredictable or decreased plasma concentrations. Both midazolam and morphine were retrospectively studied and shown to require escalating doses on a daily basis (early and late, likely secondary to an increased volume of distribution) to achieve similar clinical effects compared with non-ECMO controls (5). Clinicians frequently encounter the need for more consistent and deeper levels of sedation to avoid potentially harmful/fatal events including catheter dislodgment/malpositioning, suction events associated with ventilator dsynchrony, oxygen consumption, and optimization of flow/ventilation. The comprehensive list of aforementioned variables clearly combines to create challenges in maintaining optimal sedation in ECMO.

We present two cases of prolonged VV ECMO in which methadone was used as an adjunct to more commonly used sedation agents. Methadone is a long-acting synthetic opioid with antagonist properties at the NMDA receptor. It has been shown to improve spontaneous breathing trials and weaning from continuously infused sedation in the critically ill; however, nothing in literature has described its utility in ECMO (6). To date, ketamine and *dexmedetomidine* have been used as adjuncts that have been shown to be effective in reducing doses of benzodiazepines and opioids in ECMO; otherwise, the data are limited, especially in adult populations (7,8). These case reports were approved by our medical center's Institutional Review Board.

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CLINICAL EXAMPLES

A 23-year-old male (body mass index 29.9) with no known past medical history presented to a community hospital with

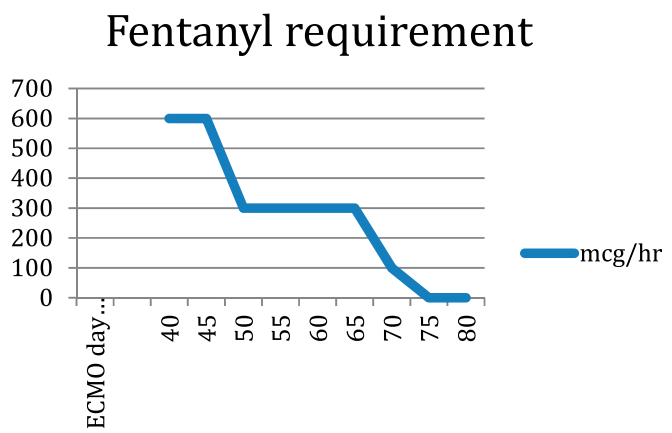

Figure 1. Demonstrates the decreasing requirements of fentanyl during the clinical course after the initiation of methadone.

multi-day history of fever, cough, and shortness of breath. As he developed severe ARDS, he was transferred to our cardiac surgery intensive care unit for ECMO evaluation. Although the specific diagnosis was never made, we presume the etiology of the patient's respiratory failure to be viral pneumonitis which was later complicated by a superimposed bacterial pneumonia. On admission, the patient's respiratory cultures, antibody, and autoimmune testing were all negative. Nine days after the onset of symptoms, he was cannulated with a veno-venous dual-chamber Avalon cannula (Avalon Laboratories, Rancho Dominguez, CA) in the right internal jugular vein for refractory hypercapnia/hypoxemia. The patient required very high doses of sedatives/opiates as he demonstrated clinical signs of tolerance as a result of prolonged exposure. Within a few days, he required continuous infusions of hydromorphone (9 mg/h), fentanyl (500 mcg/h), propofol (100 mcg/kg/min), versed (10 mg/h), dexmedetomidine (1.2 mcg/kg/h), and quetiapine (150 mg 3 times a day [TID]). Clinical events leading to varying doses of sedation/analgesia included cannula malpositioning with resultant hypoxemia, ventilator dsynchrony, tachycardia (can lead to shunting in VV ECMO), multiple bronchoscopies, gastrointestinal bleeds necessitating esophagogastroduodenoscopy, hypertension, re-intubation, suction events, tracheostomy, seizure activity, circuit exchanges, and pneumothorax requiring tube thoracostomy, thoracentesis, and laparascopic cholecystectomy. Three weeks into the clinical course methadone (30 mg intravenous 4 times a day/40 mg by mouth 4 times a day) was introduced and other sedation was eventually weaned off (77 days after methadone) (see Figures 1–3). After 118 days of cannulation, the patient was in the process of tapering off methadone (10 mg intravenous 4 times a day/30 mg by mouth at night) while awaiting lung transplant. He eventually encountered refractory septic shock and died.

A 28-year-old female (BMI 29.3) with a history of Crohn's disease and ileocolonic stricture was admitted for a 2-week history of constipation. She was taken to the gastrointestinal suite for colonoscopy and dilation of the stricture, during which she aspirated feculent material. This led to severe hypoxemia and, on the same day, she was placed on VV ECMO. Despite fentanyl (800 mcg/h), midazolam (3 mg/h), dexmedetomidine (1.7 mcg/kg/h), and olanzapine (5 mg intravenous at night), the patient remained in distress (likely due to tolerance over time), and methadone was started (10 mg intravenous 3 times a day/40 mg by mouth 3 times a day) three weeks post-cannulation. The clinical course was complicated by multiple laparotomies/wound vac exchanges, septic shock, bronchoscopies, cannula malpositioning, thoracentesis, hemothoraces, video assisted thorascopic surgery, circuit exchanges, renal failure, gastrointestinal bleed, and heart block. The introduction of methadone resulted in decreases in number/dosages of infusions, and on ECMO day 43, the propofol was weaned off with fentanyl maintained (100 mcg/h) (see Figures 3 and 4). While awaiting lung transplantation, the patient experienced profound hypotension due to septic shock and pericardial effusion and died on ECMO day 51.

DISCUSSION

We present two cases demonstrating the effective use of methadone as an adjunct for patients on ECMO for

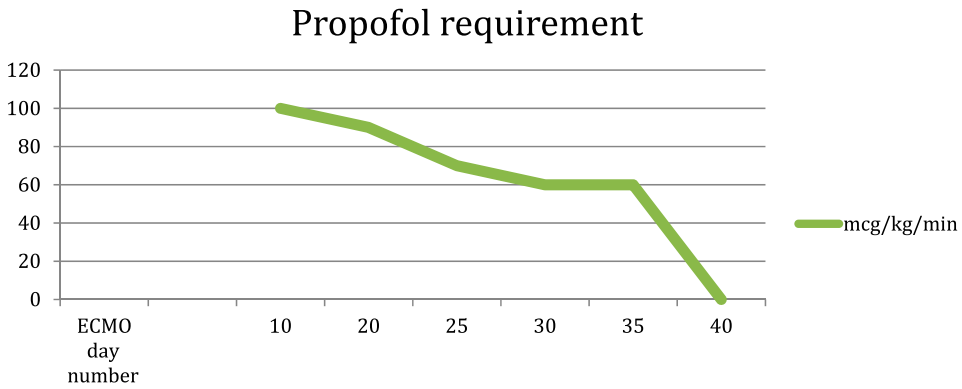

Figure 2. Demonstrates the decreasing requirements of propofol during the clinical course after the initiation of methadone.

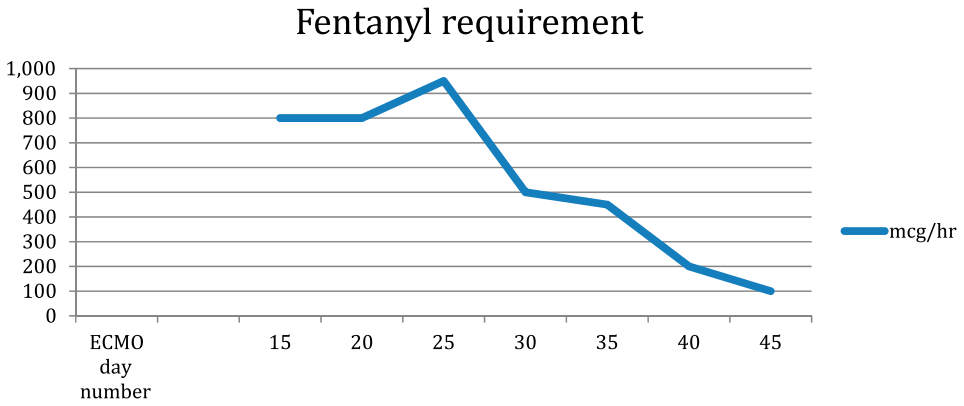

Figure 3. Demonstrates the decreasing requirements of fentanyl during the clinical course after the initiation of methadone.

a prolonged period of time. There is growing recognition and evidence that patients can survive long courses of VV ECMO. As the duration lengthens, so do the challenges associated with sedation management. Agents that are typically used in the Intensive Care Unit may be well suited for short-term non-ECMO patients, but their unpredictable pharmacokinetics and need for continuous dose escalation (as signs and symptoms of tolerance become apparent) during long runs of ECMO are problematic.

VV ECMO using the Avalon dual-chamber cannula allows for simultaneous drainage and return of blood after being sent through an oxygenator/artificial lung membrane. While serving as rescue therapy for patients in respiratory failure, the addition of an oxygenator, pump, tubing, and cannula to the circulatory system significantly alters dosing requirements of many administered medications including sedatives. While on VV ECMO, clinicians must be considerate of drug extraction by the circuit, increased volume of distribution, and the various degrees of multi-organ dysfunction and failure (9).

In January 2013, the Society of Critical Care Medicine published the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (10). The goal is to decrease delirium by effectively treating pain while avoiding over sedation with a view to active participation in care, early mobilization, and improved outcomes (10). Highlighting the importance of such initiatives, Brodie et al. recently published evidence demonstrating that physical therapy is not only crucial but also safe in ECMO patients; however, it does require patient ability to participate (11).

Methadone is a long-acting opioid often used in the management of chronic pain and opioid dependence. We demonstrated its effective use in decreasing other opiates and sedatives without the need for dose escalation in patients. Methadone's hydrophilic propensity and degree of protein binding explain its potential benefit as a preferred sedative in this patient population. Our positive experience must however be tempered with an appropriate understanding of the potential for adverse events. Methadone

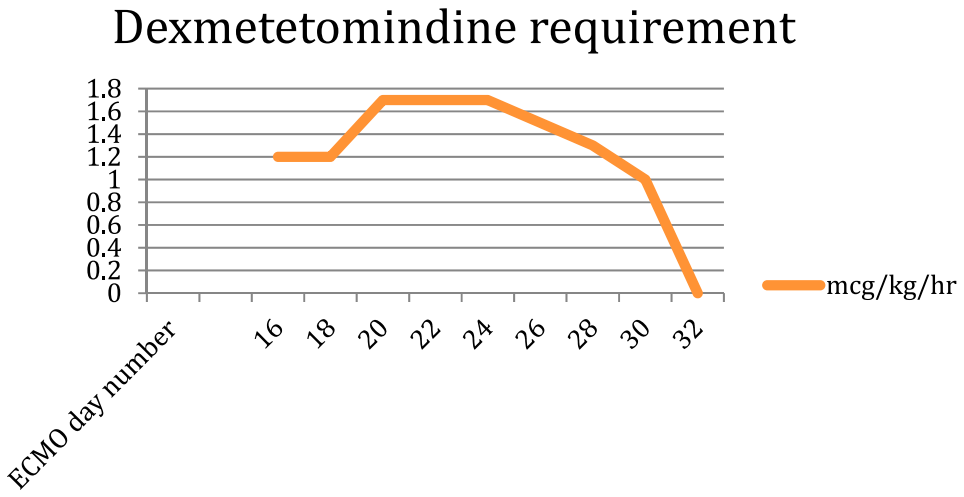

Figure 4. Demonstrates the decreasing requirements of dexmedetomidine during the clinical course after the initiation of methadone.

should be used cautiously in those at risk for serotonin syndrome and decompensated cardiopulmonary failure (12). We suggest that methadone be reserved for use in ECMO patients who are requiring high doses of sedatives, demonstrate tolerance, and need long-term support.

The considerations of drug variability, ECMO physiology, and dynamic clinical stability create a challenging dilemma in the control of pain, agitation, and delirium. Although studies hypothesize theories behind variability, there is little in the form of protocols or alternative agents that serve as adjuncts. We report the successful use of methadone during ECMO and suggest its use in select patients.

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