Sedation during extracorporeal membrane oxygenation—why more is less

Patients on extracorporeal membrane oxygenation (ECMO) often have increased sedation requirements\(^1\). Given the expanding scope of ECMO\(^2\) and increasing awareness of the morbidity associated with excessive sedation in the intensive care unit\(^3\), it is important that the mechanisms behind such altered sedation needs are further investigated. To that end, we measured the plasma concentrations of morphine, midazolam and their clinically relevant metabolites prior to and after the commencement of ECMO in a patient with preserved hepatic and renal function in order to highlight the independent effect ECMO may have on the pharmacokinetics of these compounds. Prior ethics approval was obtained from the local Human Research Ethics Committee (HREC/11/QPCH/121).

A 30-year-old man (admission weight 85 kg) with severe respiratory failure was referred to the Prince Charles Hospital, Brisbane, Queensland, for consideration for venovenous ECMO as a bridge to recovery or lung transplantation. He had been ventilated for 20 days for a biopsy-proven cryptogenic organising pneumonia that was not responsive to immunosuppression. Sedation prior to and after commencement of ECMO was titrated to a Richmond Agitation Sedation Scale of -3 to -4 and a bispectral index of 40–45. The patient also received neuromuscular paralysis with vecuronium (0.5 mg/hour, titrated to 1–2 twitches on train-of-four monitoring) to optimise ECMO flows and ventilation. Pre-ECMO sedation comprised of propofol 100 mg/hour, morphine 20 mg/hour and midazolam 20 mg/hour. Percutaneous cannulation was performed using a 25 Fr multistage cannula and a 22 Fr single stage cannula (Bio-Medicus\(^8\), Medtronic, Minneapolis, MN, USA) in the left and right femoral veins for access and return, respectively. The circuit consisted of biolone tubing, a centrifugal pump and a polymethyl pentene oxygenator (Jostra Rotaflow\(^9\) & Quadrox D\(^6\), Maquet, Germany). Serial blood samples (1 ml) from a radial arterial line were collected over a 90-minute period prior to and 12 hours after commencing ECMO for measurement of the plasma concentrations of morphine, midazolam and their major metabolites. Samples were analysed using a validated robotic solid phase extraction liquid chromatography-tandem mass spectrometry method.

In the first three hours after commencement of ECMO, the propofol infusion regimen was increased to 200 mg/hour (\(P=0.4\)), and the morphine and midazolam infusion regimens were each increased to 50 mg/hour (\(P <0.001\)) to achieve pre-ECMO sedation levels (Figure 1A). In addition, propofol was also administered as repeated boluses (30–50 mg, up to total of 300 mg in the first hour). The escalation in morphine and midazolam doses correlated with a decrement in plasma concentrations of these drugs and their active metabolites. There was a significant reduction in the plasma morphine (20%), midazolam (11%), 1-hydroxy midazolam (17%), morphine-3-glucuronide (36%) and morphine-6-glucuronide (35%) concentrations on commencement of ECMO, compared to pre-ECMO levels which increased consistently with the marked increase in administered drug doses (Figures 1B and 1C). The increased requirement for sedation persisted for the entire duration of ECMO (19 days). Tracheotomy performed on day 7 did not lead to a significant reduction in sedative doses.

Despite studies showing heightened sedation requirements during ECMO\(^1\), the mechanisms underpinning this clinical observation are not adequately defined. Pharmacokinetics studies in neonates have reported increased volumes of distribution and decreased drug elimination during ECMO\(^3\).
In vitro circuit studies using neonatal circuits show significant sequestration of sedative and analgesic drugs in the ECMO circuit. However, this pharmacokinetics data cannot be extrapolated to adults due to physiological and technical differences between the two populations. More detailed reviews of the sparse data on altered pharmacokinetics during ECMO can be found elsewhere.

The altered sedation requirements in this cohort is concerning as excessive sedative drug use may add to intensive care unit morbidity. However, achieving optimal levels of sedation to promote comfort, relieve stress, maximise ECMO flows and minimise oxygen consumption, while preventing accidental dislodgement of life-sustaining equipment, can be a difficult balancing act in the setting of altered pharmacokinetics during ECMO. Although the use of minimal sedation and early tracheotomy and ambulation in selected patients has been reported, this is not always possible.

This report provides preliminary mechanistic explanation for altered sedation requirements in these patients on ECMO. It also highlights important clinical issues such as sedation targets during ECMO, utility of bispectral index monitoring and the timing of tracheotomy in critically ill patients receiving ECMO. Systematic research using ex vivo animal and clinical pharmacokinetic studies is required to improve sedative and analgesic drug prescription during ECMO.

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