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Can optimal drug dosing during ECMO improve outcomes?

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Dear Editor,

Abrams et al. [1] in their recent article identify pharmacokinetics (PK) of medications during extracorporeal membrane oxygenation (ECMO) as a potential area to be explored in future trials. As highlighted by the authors, the use of ECMO in severe ARDS remains controversial. Currently, it is still unclear if the unquantified risks of ECMO outweigh the risks of persisting with lung protective ventilation in a patient with refractory hypoxaemia. The future of ECMO in general may thus rely on research aimed at minimising the risks posed by this invasive intervention itself.

ECMO plays a supportive role in ARDS and the outcomes rely heavily on reversibility of the underlying lung condition. A majority of patients who undergo ECMO for ARDS are either diagnosed with or presumed to have viral and/or bacterial pneumonia upon presentation and receive targeted or broad-spectrum antibiotic therapy in an attempt to reverse their pulmonary pathology. A significant proportion of them also develop secondary infections while on ECMO. However, the ECMO system itself may induce significant PK alterations [2] in a critically ill patient who already has profound alterations in PK, resulting in suboptimal plasma antibiotic concentrations and compromised outcomes. Similarly, ECMO can variably affect the bioavailability of any drug based on their physicochemistry and type of ECMO circuitry used [2, 3]. While sedative, inotrope, vasopressor, diuretic and anticoagulant therapy can be titrated to measurable end points, no real time targets exist for antibiotic drugs. The absence of routine therapeutic drug monitoring for most antibiotic drugs raises significant concerns regarding the use of standard dosing regimes in ECMO patients.

However, the independent effects of the ECMO circuit on PK are difficult to quantify in a critically ill patient. An incremental approach that incorporates PK studies in simulated ECMO circuits, large animal models of ECMO and clinical subjects may provide an advanced understanding of drug, device and disease factors affecting PK during ECMO and enable the development of evidence-based guidelines for drug dosing in these complex patients. Mechanistic PK studies in ex vivo ECMO circuits and in ovine models of ECMO are currently underway [4]. This platform is also being utilised by our group to systemically investigate the effects of ECMO on pathophysiology, inflammation, coagulation, pulmonary and other organ functions, and nutrient disposition. An international multi-centre, population PK study [5] is currently recruiting, and vital PK data will soon be available for 18 important antibiotic, sedative and analgesic drugs commonly prescribed during ECMO. This may lead to the generation of evidence-based guidelines for dosing of the above drugs during ECMO.

Exteriorising up to two thirds of patients' cardiac output into the ECMO circuit as well as exposing certain tissue beds to unusually high blood flows or oxygen tensions is non-physiological and not without risks. Despite this, current outcomes are promising, and further improvements in technology and its clinical application may shift the balance in favour of ECMO.

Conflicts of interest None.

References

1. Abrams D, Brodie D, Combes A (2013) What is new in extracorporeal membrane oxygenation for ARDS in adults? Intensive Care Med. doi: 10.1007/s00134-013-3035-4
2. Shekar K, Fraser JF, Smith MT, Roberts JA (2012) Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care 27(6):741.e9–18
3. Shekar K, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, Ghassabian S, Wallis SC, Fung YL, Smith MT, Fraser JF (2012) Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care 16:R194
4. Shekar K, Roberts JA, Smith MT, Fung YL, Fraser JF (2013) The ECMO PK Project: an incremental research approach to advance understanding of the pharmacokinetic alterations and improve patient outcomes during extracorporeal membrane oxygenation. BMC Anesthesiol 13:7
5. Shekar K, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, Ghassabian S, Wallis SC, Levkovich B, Pellegrino V, McGuinness S, Parke R, Gilder E, Barnett AG, Walsham J, Mullany DV, Fung YL, Smith MT, Fraser JF (2012) ASAP ECMO: antibiotic, sedative and analgesic pharmacokinetics during extracorporeal membrane oxygenation: a multi-centre study to optimise drug therapy during ECMO. BMC Anesthesiol 12:29

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