Original Article

Crit Care & Shock (2013) 16:8-11

Vincristine and daunorubicin administration in an adolescent during ECMO

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Abstract

***Objective*: To describe the administration of vincristine and daunorubicin to a 14-year-old girl requiring ECMO support due to a non-Hodgkin's lymphoma mediastinal mass.**

***Design and Setting*: Patient case report in an 18-bed level 1 medical-surgical Pediatric Intensive Care Unit (PICU) in a free standing children hospital.**

***Patients*: A 14-year-old adolescent female admitted to the PICU. Each author's Institutional Review Board deemed this project exempt.**

***Results*: A 14-year-old previously healthy adolescent girl presented with a 3 month history of progressively worsening respiratory difficulties. A large mediastinal mass and pleural effusion were found on computerized tomography (CT) scan. Soon after, the patient had multiple cardiac arrests and resuscitations and was deployed on ECMO. The treatment protocol for her lymphoma included high dose methylprednisolone, vincristine, and daunorubicin. The administration of all medications for this patient, including her chemotherapeutic agents, was done during concurrent use of ECMO and hemofiltration dialysis.**

***Conclusion*: Administration of vincristine during ECMO has rarely been described, and this is the first description of use of daunorubicin with ECMO. Since daunorubicin has a rapid and extensive distribution into tissues, a large volume of distribution, modest protein binding, and mainly hepatic metabolism, dosing adjustment was not necessary during ECMO. Vincristine is also rapidly and extensively distributed throughout the body, has a large volume of distribution, and undergoes hepatic metabolism. However, because of its relatively large protein binding and potential for binding in the membrane oxygenator, the vincristine dose was increased by 25% over the standard protocol. There is little published information regarding dosing of medications during ECMO, especially daunorubicin and vincristine, and even less during ECMO with concurrent hemofiltration dialysis. Additional studies are needed to optimize medication dosing during ECMO.**

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Key words: Extracorporeal membrane oxygenation, chemotherapy, pediatric critical care, oncology.

Introduction

Though historically rooted in surgery for congenital heart disease, extracoproreal membrane oxygenation (ECMO) has evolved over the years from use in the operating room to the intensive care unit and from treating neonates with congenital heart disease to supporting a broad range of ages and disease processes. (1) ECMO has now been used for greater than 30 years, and in over 50,000 patients worldwide.

While neonates remain the largest portion of patients utilizing ECMO with over 30,000 documented cases, use in the pediatric population accounts for over 12,000 cases. (2) Multiple etiologies for multisystem organ failure is documented as leading to the use of ECMO, including myocarditis, congenital heart disease, sepsis, malignancy and mediastinal mass. (3)

Despite this number of the most critically ill patients, there is a paucity of published literature describing how the pharmacokinetic parameters of drug binding, volume of distribution, and drug elimination are altered with ECMO, either alone or with concurrent hemodialysis. A literature search reveals very limited reports describing chemotherapeutic agents used during ECMO, and to our knowledge, none specifically detailing the use of daunorubicin in a patient on ECMO.

Case report

This is a retrospective case report in which we describe our experience treating a 14 year female, newly diagnosed with non-Hodgkin's lymphoma, with vincristine, and daunorubicin while on ECMO and continuous renal replacement therapy (CRRT) for multiorgan system failure. She was treated in our 18-bed medical-surgical pediatric intensive care unit (PICU) in our free standing tertiary care children hospital. Each author's Institutional Review Board deemed this project exempt.

Our patient presented with a three month history of progressively worsening respiratory difficulties and acute shoulder pain. A large mediastinal mass and pleural effusion were noted on computerized tomography (CT) scan obtained at presentation (**Figure 1**), and she was subsequently diagnosed with non-Hodgkin's lymphoma. Initial treatment included placement of a chest tube and drainage of three liters of fluid from her thorax. Shortly after this procedure, she decompensated, and suffered a full cardiac arrest. Despite prolonged resuscitation efforts, she did not regain cardiopulmonary stability and was deployed on ECMO, comprised of a centrifugal pump and a hollow fiber oxygenator.

After initiating full support with veno-arterial ECMO, she progressed to multiorgan system failure, including renal failure, and a dialysis filter for CRRT was added to the circuit. The use of ECMO and a hemodialysis circuit complicated the dosing of her medications, including the chemotherapeutic agents. The treatment protocol for non-Hodgkin's lymphoma in our patient included high dose methylprednisolone, vincristine, and daunorubicin.

Changes in pharmacokinetics on ECMO

It is known that during ECMO the pharmacokinetic parameters of drug agents are altered, some significantly. On the initiation of ECMO, patients must be given large volumes of exogenous blood to compensate for the circuit volume, increasing the extracellular fluid compartment. This, along with disease state alterations in kinetics, can increase the volume of distribution of drugs given to the child requiring dosing increases of water soluble drugs (e.g. gentamicin). (4) Additionally, because of the large surface area of the tubing used to accomplish this form of circulation, medications may be adsorbed onto the circuit decreasing the pharmacologic affect. (4)

The reservoir or bladder is a component of the tubing that allows for the trapping of air bubbles and potential clots, but can also trap drugs delaying drug delivery. (4) A permeable membrane allows for the addition of oxygen into the blood supply in the circuit and can also trap drugs in the process. Most patients will have a decreased renal function on ECMO necessitating a longer dosing interval of renally excreted drugs. The addition of a dialysis filter to the circuit allows for CRRT and can also bind drugs.

Vincristine pharmacokinetics

Vincristine is a vinca alkaloid chemotherapeutic agent which has been used in pediatric acute lymphoblastic leukemia (ALL) since 1962. (5) The distribution of vincristine is rapid, extensive and has a high volume of distribution of 15 L/kg, is eliminated in the feces, and has an half-life of

approximately 15 hours. (5) Vincristine has approximately 75% albumin binding, which was the only parameter that would necessitate a potential change in dose. (6) Secondary to the potential binding of the vincristine in the circuit, the dose of vincristine was increased to 2.5 mg from the standard protocol dose of 2 mg, similar to a previous report using ECMO. (7)

Daunorubicin pharmacokinetics

Daunorubicin is an anthracycline antibiotic used in the treatment of leukemia since its introduction in the 1960's, but it is often limited by its propensity to cause cardiotoxicity. (8) It exhibits a large volume of distribution (39.2 L/kg) and high tissue affinity (approximately 180 times higher cellular concentration than plasma). (8) It is approximately 60% protein bound (9) and has a plasma half-life of approximately 12 hours. (8) Since daunorubicin has a large volume of distribution, moderate protein binding, and a large and rapid intracellular distribution, standard dosing protocol was not changed due to ECMO.

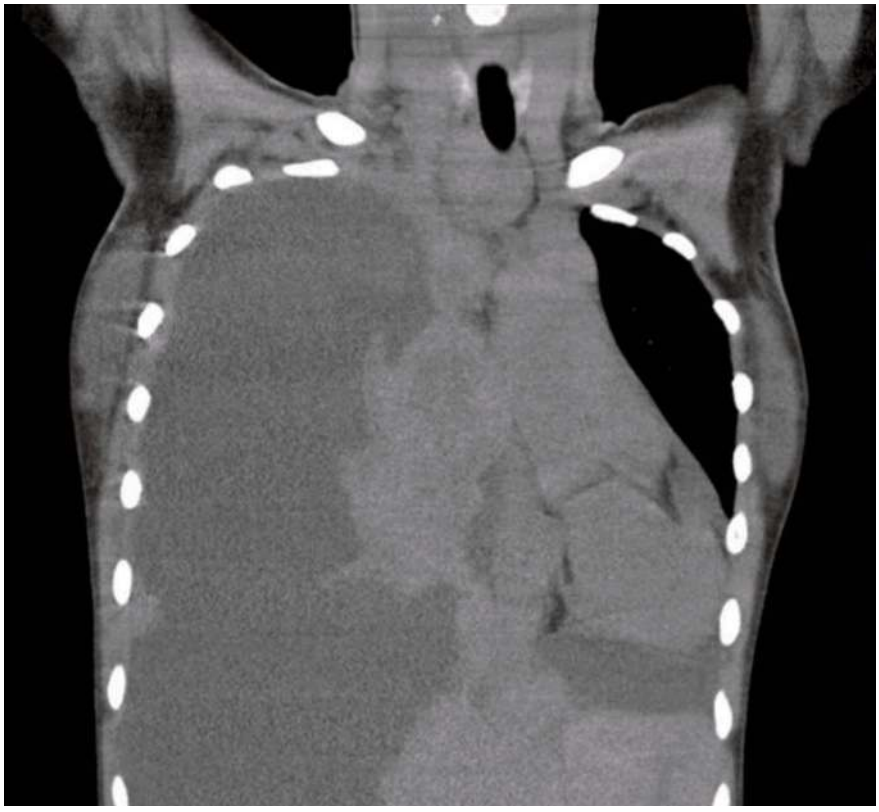
Conclusion

There is in general a lack of pediatric pharmacokinetic data with chemotherapeutic agents. This lack of data is even more pronounced when treatment is complicated by the use of ECMO, CRRT or both, and drug dosing guidance is not available for many commonly used agents. In this case, we were specifically interested in data regarding vincristine and daunorubicin, as these medications were the mainstays of therapy for the newly diagnosed non-Hodgkin's lymphoma of our patient.

Administration of vincristine during ECMO has rarely been described in the literature, and this is the first description of daunorubicin administration during ECMO. Since daunorubicin has a rapid and extensive distribution into tissues, a large volume of distribution, modest protein binding, and mainly hepatic metabolism, we did not adjust dosing for our patient. Vincristine is also rapidly and extensively distributed throughout the body, has a large volume of distribution, and undergoes hepatic metabolism. Because of its large protein binding, and one similar case report, the vincristine dose for our patient was increased by 25% over the standard protocol. This dose increase was an attempt to overcome potential binding in the ECMO circuit (tubing and oxygenator).

To the authors' knowledge, this is the first case reporting administration of daunorubicin and the second case reporting administration of vincristine during ECMO with concurrent CRRT. The population of critically ill pediatric patients on ECMO is one of our most vulnerable groups, and in order to optimize outcomes, the authors feel more data is essential. Our report is limited by having a patient number of one. Larger studies are needed to truly elucidate the pharmacokinetic parameters for many medications used in ECMO, including chemotherapy.

Figure 1. Initial chest CT scan



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