Continuous-Infusion Etomidate in a Patient Receiving Extracorporeal Membrane Oxygenation

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We describe a 16-year-old, 65-kg male deployed on extracorporeal membrane oxygenation (ECMO) for refractory respiratory failure secondary to ingestion of multiple substances. During his ECMO course, standard sedative and analgesic strategies failed and alternative medications were used. The patient received various dosages of fentanyl, morphine, hydromorphone, clonidine patches, dexmedetomidine, lorazepam, methadone, pentobarbital, olanzapine, and propofol. Despite administration of multiple agents, on day 29 of ECMO the patient experienced elevated blood pressures due to agitation, and continuous infusion etomidate was started. At the time of etomidate initiation, the osmolar gap was 8 mOsm/kg. During etomidate therapy, the blood pressure remained normal, sedative agents were slowly weaned, and the patient required few PRN medications. On day 6 of etomidate, the osmolar gap increased to 127 mOsm/kg and etomidate was discontinued. Continuous-infusion ketamine was started, but the blood pressure was not controlled. Metabolic acidosis is a known side effect of etomidate due to inclusion of propylene glycol as a pharmaceutical solvent in the formulation. Despite high-dose etomidate (20 mcg/kg/min) for approximately 6 days, our patient did not experience metabolic acidosis. Absence of this adverse effect caused us to question the role of the ECMO circuit. To our knowledge, this is the first report of the use of continuous-infusion etomidate during ECMO. Etomidate infusion could be considered in difficult-to-manage patients after other alternatives have failed.

ABBREVIATIONS BUN, blood urea nitrogen; ECMO, extracorporeal membrane oxygenation.

KEYWORDS case report; ECMO; extracorporeal membrane oxygenation; etomidate; propylene glycol toxicity; respiratory failure

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Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced form of life support that is used to facilitate oxygen delivery in cases of refractory respiratory failure and for hemodynamic support in cardiac failure. Multiple pharmacokinetic alterations affect drug dosage during ECMO.¹ Sedation and analgesic management can be a challenge secondary to the binding of many agents to the ECMO circuit.¹ We describe the use of continuous-infusion etomidate during ECMO in a difficult-to-sedate patient.

Case

We previously described a 16-year-old (65 kg) previously healthy male deployed on ECMO for refractory respiratory failure.² In brief, he was admitted to an outside hospital after an ingestion of baclofen, promethazine, alcohol, and marijuana. After 2 weeks at the outlying facility he was transferred to our level 1 Pediatric Intensive Care Unit for further management. Secondary to worsening hypoxia and air leak syndrome on mechanical ventilation, venovenous ECMO was initiated on day 13 (day 31 after ingestion and ventilation).

Venovenous ECMO was chosen because the patient had good cardiac function with an ejection fraction of 67.8% prior to ECMO initiation. The ECMO circuit consisted of a Sorin CP5 (Sorin Group USA Inc, Arvada, CO) revolution cone with a Maquet Quadrox (Maquet Cardiovascular LLC, Wayne, NJ) oxygenator with flow set to 2235 revolutions per minute, resulting in a 4 L/min average blood flow.

On day 24 of ECMO the patient experienced an increase in blood pressure (150/95 mm Hg) secondary to agitation. Proper sedation and analgesia had been difficult to achieve despite escalating doses of multiple agents, including fentanyl and hydromorphone. His blood pressure management included nicardipine (7 mcg/kg/min), and 2 clonidine transdermal patches 0.2 mg per 24 hours each for a total of 0.4 mg per 24 hours applied weekly.

His medications on day 24 consisted of olanzapine 10 mg, morphine 1 mg/kg/hr (65 mg/hr), midazolam 0.36 mg/kg/hr (23.4 mg/hr; titrated down from 0.72 mg/kg/hr after suspected paradoxical increased agitation), methadone 10 mg intravenously (IV) every 12 hours, lorazepam 10 mg IV every 4 hours, and dexmedetomidine 3 mcg/kg/hr (titrated up from 0.7 mcg/kg/hr after little effect).

In addition, sedative/analgesics were being administered frequently for agitation (i.e., morphine 35 mg, midazolam 15 mg, and pentobarbital 50 to 100 mg were given every hour as needed). The patient continued to experience episodic agitation with concurrent elevations in blood pressure, and a continuous infusion of propofol was initiated and titrated up to 75 mcg/kg/min. Triglycerides at this time were 90 mg/dL. Throughout the patient's course, renal function remained adequate with normal serum creatinine, but liver enzymes were mildly elevated.

On day 29 the patient developed potential rebound agitation from midazolam; hence, the midazolam was decreased to 0.18 mg/kg/hr (11.7 mg/hr) and morphine was increased to 1.2 mg/kg/hr (78 mg/hr). Despite propofol, his blood pressure remained elevated (140/90 mm Hg), with episodic spikes up to 170 mm Hg systolic. The patient's triglycerides became elevated (474 mg/dL); therefore, the propofol was discontinued. At this time, his as needed medications included midazolam 20 mg IV, morphine 35 mg IV, pentobarbital 75 mg IV, lorazepam 10 mg IV, and methadone 10 mg IV. Each was given hourly as needed, with the patient requiring about 10 doses per day. Because other agents failed to control agitation, continuous infusion etomidate was started at 5 mcg/kg/min and was rapidly titrated to 20 mcg/kg/min. Because propylene glycol is the pharmaceutical solvent in lorazepam and etomidate, serum osmolality was monitored. At the start of therapy, the patient's measured and calculated serum osmolalities were 314 mOsm/kg and 306 mOsm/kg (normal = 285-295 mOsm/kg), respectively. The patient's blood urea nitrogen (BUN) concentration of 79 mg/dL (osmolar gap of 8 mOsm/kg) contributed to the calculated osmolality.

For the next 6 days the patient had excellent blood pressure control, with averages of 100/75 mm Hg and with little to no use of PRN medications (approximately 0-1 doses per day). Continuous infusions were decreased: midazolam to 0.06 mg/kg/hr (3.9 mg/hr), dexmedetomidine to 1.5 mcg/kg/hr, and morphine to 1 mg/kg/hr (65 mg/hr).

On day 35 of ECMO (day 6 of etomidate) the patient's measured serum osmolality was 446 mOsm/kg, with a calculated serum osmolality of 319 mOsm/kg (BUN elevated at 97 and osmolar gap of 127 mOsm/kg).

Although the patient did not have manifestation of toxicity (e.g., acute kidney injury), because of concerns that the propylene glycol contained in the etomidate infusion was responsible for the osmolar gap, etomidate was discontinued and ketamine was started and titrated up to 15 mcg/kg/min. Unfortunately, there was a subsequent loss of blood pressure control, as it returned to 150/90 mm Hg, and PRN medication use returned to 15 doses per day. Twelve hours later a repeat osmolality revealed a decrease to 427 mOsm/kg, with a slight increase in the calculated osmolality to 326 mOsm/kg (osmolar gap of 101 mOsm/kg). Twenty hours after

the etomidate infusion was discontinued, a propylene glycol level was obtained and sent to a reference laboratory. The resultant value was 450 mg/dL. During the time of the etomidate infusion, the patient's blood pH remained normal and he was not acidotic, nor did he exhibit clinical signs of propylene glycol toxicity.

Discussion

Etomidate is a short-acting benzylimidazole hypnotic used in general anesthesia. It has a rapid onset of action (30 seconds) and a short duration of action (2-10 minutes) that is dose dependent. It is generally given as a loading dose of 0.2 to 0.3 mg/kg over 30 seconds. Continuous infusions are not common, but doses of 1 to 25 mcg/kg/min have been reported.^{3,4} It has a large volume of distribution, undergoes renal elimination (75% [80% as metabolite, 2% as unchanged drug]), and is about 80% protein bound to albumin.⁵

Etomidate is primarily used during rapid-sequence intubation in pediatric patients. In a study of 77 pediatric patients in the emergency room, endotracheal tube placement was successful in 99% of those given etomidate for rapid sequence intubation.⁶ The authors concluded that etomidate was a useful agent and that it was associated with infrequent hypotension.⁶ In another study of 84 pediatric patients who underwent rapid-sequence intubation using etomidate there were no statistically significant changes in blood pressure or clinically important adrenocortical suppression.⁷

The major side effect and concern in the use of etomidate is its ability to inhibit 11 β -hydroxylase, which decreases cortisol, aldosterone, and corticosterone, leading to adrenal suppression.^{8,9} This suppression can last up to 72 hours after a single dose of etomidate. In fact, an adult who received a 20-hour infusion of etomidate (1.3-1.5 mg/kg/hr) had marked adrenocortical suppression that was evident 4 days after etomidate was discontinued.⁸ For this reason, continuous infusion is not recommended by the manufacturer,¹⁰ especially in critically ill patients where etomidate exposure was noted to be an independent risk factor for adrenal insufficiency.¹¹ Despite 6 days of continuous etomidate, our patient showed no signs of adrenal insufficiency. The lack of adrenal insufficiency may be due to the concurrent administration of methylprednisolone (5 mg IV every 12 hours) for pulmonary inflammation. Levy et al¹² reported that administration of dexamethasone 2 mg IV daily successfully prevented adrenocortical insufficiency in 3 patients given continuous-infusion etomidate.

To our knowledge this is the first report of prolonged administration of continuous-infusion etomidate for sedation management in a difficult-to-control patient receiving ECMO. Because of its pharmacokinetic parameters of renal elimination and large protein binding, etomidate is unlikely to be extensively removed from the ECMO circuit; however, the moderately large

protein binding may confer some binding in the circuit tubing. Had this occurred, it may explain the need for a rapid titration in dose in order for this patient to show a clinical response. However, because this patient was resistant to most other therapies, administration of a large dose of etomidate may simply have been a reflection of pharmacodynamics response in this patient.

The etomidate 2 mg/mL product contains 35% propylene glycol, which is used as a pharmaceutical solvent. Propylene glycol is a small-molecular weight alcohol, 76.1 Da, that is nonionic, is highly water soluble, and lacks significant serum protein binding. Its accumulation can cause toxicity that consists of hyperosmolality, hemolysis, anion gap metabolic acidosis, cardiac arrhythmia, seizure, coma, and hypotension.¹³ An osmolar gap of greater than 10 mOsm/kg can signify excess propylene glycol in the body, with a propylene glycol level of greater than 18 mg/dL being consistent with toxicity.¹⁴

In a case series, 7 patients were randomized to pentobarbital or etomidate for refractory cerebral edema.¹² Three patients (two adults and one 14-year-old) received a 0.30 mg/kg IV induction of etomidate and then 0.02 mg/kg/min continuous infusion for 24 to 72 hours titrated to burst suppression. All patients developed renal compromise and had increased serum osmolality within 24 hours of administration; hence, the study was terminated.

A 9-year-old who received 12 hours of a continuous infusion of etomidate had an increase in serum osmolality, metabolic acidosis, and hemolysis that was associated with a measured propylene glycol level of 230 mg/dL.¹⁵ In this case, the propylene glycol level would likely have been higher, but the patient received 2 exchange transfusions during the infusion.¹⁵

Our patient had an increased serum osmolality (measured and calculated) at baseline due to an increased BUN. Because the patient was also on IV lorazepam every 4 hours, serum osmolality was obtained prior to starting etomidate, and there was no real gap between the measured and calculated values. On day 6 of etomidate therapy there was a 127 mOsm/kg gap between the measured and calculated osmolalities, and the etomidate infusion was discontinued. During the infusion he received an estimated 275 mL of propylene glycol per day. Twelve hours after discontinuing the etomidate the measured osmoles dropped by 19 mOsm/kg, and the gap decreased by 26 mOsm/kg, but the calculated gap increased as a result of an increased BUN. Following 6 days of continuous-infusion etomidate and after discontinuation of the etomidate, his propylene glycol serum concentration was 450 mg/dL. This change was likely a direct result of the etomidate discontinuation and renal clearance, because the patient was not on hemodialysis.

Considering the above osmolar gap and the patient's propylene glycol level, our patient should have devel-

oped metabolic acidosis and other adverse effects associated with propylene glycol. In a case of an 11-month-old infant with massive bupropion overdose, the patient had a pH of 7.05. Within 2 hours of ECMO initiation the patient's pH increased to 7.35.¹⁶ We speculate that the ECMO circuit may have offered some protection against propylene glycol toxicity and increasing osmolar level; however, the effects of ECMO in this arena have not been studied.

Secondary to all of the potential problems and adverse reactions with etomidate, its use in critical care is limited, and continuous infusion is generally not recommended. The ECMO circuit may have helped in decreasing the side effects of propylene glycol toxicity because this patient did not experience any, except for the increased serum osmolality.

Because of the ECMO circuit with the revolution cone, blood flow is extremely dependent on afterload and preload, making hypertension due to agitation important to control. After multiple failed attempts at control of sedation with various agents, etomidate proved to be the most successful for this patient. Etomidate should not be considered as standard sedation for the critically ill pediatric patient, but it may be considered in extremely difficult-to-manage patients after other options have failed. Extra caution must be taken to watch for adrenal insufficiency and address it as soon as possible. Like in Levy et al,¹² the prophylactic use of steroids might be considered. Cumulative doses of propylene glycol and resultant toxicity from accumulation should also be considered. The patient's serum osmolality should be monitored and etomidate should be discontinued if the patient develops an unexplained osmolar gap.

ARTICLE INFORMATION

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