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Case Report
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Successful Treatment of Propranolol-Induced Cardiac Arrest with ECMO Cardiopulmonary Resuscitation (ECPR)

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Abstract

Introduction: Propranolol toxicity causes severe cardiovascular complications, is challenging to manage, and is associated with high morbidity and mortality. Historically, successful management involves a combination of glucagon and high-dose insulin infusion. Occasionally, hemodialysis may be helpful in certain beta-blocker overdoses. In severe refractory cases, the utility and success of Extracorporeal Life Support (ECLS) have been sporadically successful internationally but rarely reported in Australian clinical practice.

Case Report: A 24-year-old female presented with in-hospital Pulseless Electrical Activity (PEA) cardiac arrest secondary to an intentional large propranolol overdose. Despite standard conventional treatment, she remained in cardiac arrest and was subsequently transitioned to Extracorporeal Cardiopulmonary Resuscitation (ECPR). She was successfully cannulated and commenced on Veno-Arterial (VA) Extracorporeal Membrane Oxygenation (ECMO) within 60 min of CPR.

Conclusion: ECPR and ECMO should be considered early in patients with refractory cardiovascular collapse secondary to significant cardiotoxicity from extensive propranolol poisoning.

Keywords: Propranolol overdose; E-CPR; ECMO; Insulin infusion; Glucagon infusion

Abbreviations

PEA: Pulseless Electrical Activity; SAAS: South Australian Ambulance Service; CPR: Cardiopulmonary Resuscitation; CTPA: Computed Tomography Pulmonary Angiography; MMSE: Mini-Mental State Examination

Introduction

Propranolol, a lipophilic β-adrenoceptor antagonist, is a first-generation β-blocker used to treat various conditions, including hypertension, cardiac dysrhythmias, anxiety, and benign essential tremors [1]. Propranolol antagonizes the β_1 and β_2 receptors with equal affinity, lacks intrinsic sympathomimetic activity, and is highly lipid-soluble with an oral bioavailability of 30% and a half-life ($T_{1/2}$) between 3 h to 5 h [2]. It is 90% protein bound with a volume of distribution (V_d) of 3.6l/kg and undergoes extensive hepatic metabolism. In addition, it also produces membrane-stabilizing effects when used in high doses by the inhibition of Na^+ currents [1,3].

Initially regarded as a safe medication, it was later criticized for its adverse side effects, non-selectivity, high protein-bound profile, and great inter individual variation in the liver's presystemic clearance, leading to significant variability in plasma concentration (~20 times) after an oral administration [3,4]. In place of this, its use has narrowed, gradually being phased out from clinical practice and replaced with newer b-blockers with greater efficacy.

Despite this, cases of propranolol toxicity continue to occur and pose a multitude of challenges to the treating clinician [5]. Often, they present with significant bradycardia and hypotension, leading to severe cardiopulmonary compromise and death. Their immediate cardiotoxicity effects include arrhythmias, refractory bradycardia, sinus pauses, cardiogenic shock, and asystole [6]. In addition, its negative inotropy and chronotropy effects exacerbate shock states that progress quickly into multi-organ failure.

In the past, high-dose insulin infusion and glucagon have been utilized to circumvent the antagonized β-adreno receptor to stimulate cardiac contractility. These approaches, separately

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and together, have been documented as successful strategies in the medical literature. The high-dose insulin infusion primarily exerts Ca^{2+}-dependant and independent positive inotropy [7] effects *via* the phosphatidylinositol-3-kinase dependent pathway. On the other hand, glucagon activates the adenylyl cyclase pathway, converting adenosine triphosphate to cyclic Adenosine Monophosphate (cAMP), leading to altered calcium ion influx, thus augmenting contractility.

While these modalities have been trialed and their efficacy is proven in clinical practice as reported in several case studies [8,9], the utility of ECPR and ECMO for propranolol toxicity in Australia has not been documented in the medical literature over the last ten years.

We report on the vital role of ECLS in the resuscitation of severe propranolol toxicity and demonstrate the survival benefit derived from its use. In addition, the impact of commencing ECPR and ECMO in the early phases of resuscitation contributed to a shorter Intensive Care Unit (ICU) admission and greater overall survival.

Case Presentation

Our patient, an independent 24-year-old lady with a background of borderline personality disorder, is well known in the community for repeated presentations to the Emergency Department (ED) with multiple suicidal attempts in the past. She otherwise has minimal co-morbidities and does not suffer from chronic medical illnesses.

She was brought into the hospital *via* ambulance services after she admitted to ingesting 60 tablets of immediate-release propranolol hydrochloride (40 mg per tablet; 2400 mg in total) with three tablets of Diazepam (5 mg per tablet) at noon while being in a mental health facility voluntarily. She arrived in the Emergency Department (ED) at 1408 with the following vitals: Blood Pressure (BP) of 149/90 mmHg, Pulse Rate (PR) of 81 beats per minute, Respiratory Rate (RR) of 16 breaths per minute with a Glasgow Coma Scale (GCS) of 3/15 (Eye-1 Voice-1 Movement-1). Her vitals continue to plummet with a BP of 50/20 and a HR of 40 beats per minute.

Within minutes, she developed transient generalized tonic-clonic seizures lasting for 10 sec before becoming apnoeic and progressing into a Pulseless Electrical Activity (PEA) cardiac arrest. She was intubated and CPR was commenced immediately. Overall, she had two separate periods of PEA arrest interspersed by a short period of Return of Spontaneous Circulation (ROSC) lasting 8 min.

The first PEA arrest occurred over 4 min, and the second continued for 74 min before she was commenced on ECMO. She also received three separate boluses of Intravenous (IV) Actrapid 70 units, IV calcium chloride 10 mmol, 500 mmol of IV 8.4% sodium bicarbonate, and 50 ml of IV Lipid emulsion (Lipidor) throughout the resuscitation. Despite the aggressive intervention, she remained in refractory PEA arrest, and thus E-CPR was activated 60 min into the second cardiac arrest (Figure 1).

While E-CPR was being established, her left femoral artery was cannulated with a 17Fr Maquet catheter while the right femoral vein received a 25Fr Maquet catheter. Then, she was placed on the Maquet Cardio help ECMO machine with the following settings: 2300 revolutions per minute (rpm) generating a 3 Liter (L) flow, with a fresh gas flow of 3L per minute. CPR ceased once she transitioned onto the ECMO circuit successfully.

In the Intensive Care Unit (ICU), she remained on ECMO for a total of two days before successful decannulation in the operating theatre. During this time, the ECMO settings remained relatively the same without any significant complications encountered either from the machine or the large-bore cannula apparatus.

As per standard practice, a high-dose insulin infusion was started at 0.5 to 1 unit/kg/h, amounting to an infusion rate of 70

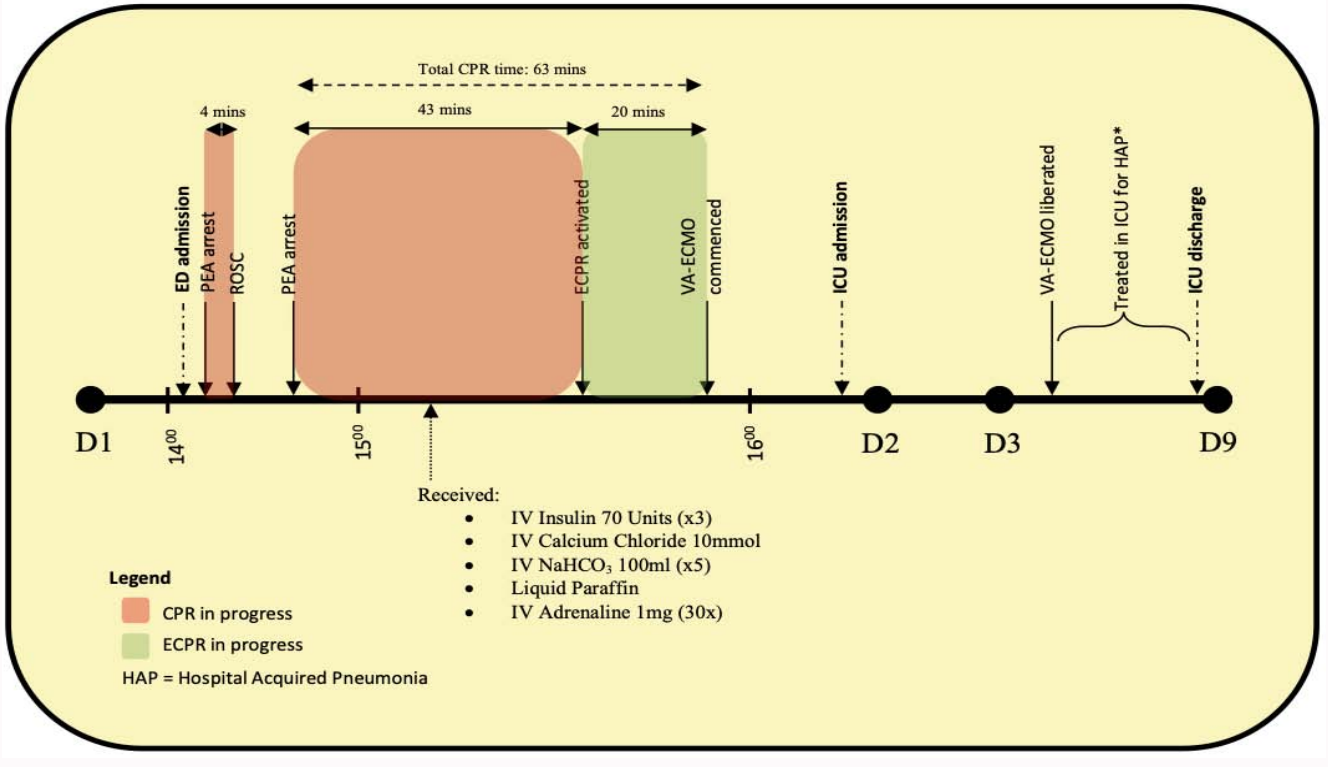

Figure 1: Timeline depicting initial resuscitation involving CPR and sequence of events leading to the initiation of ECPR.

units/h to 85 units/h, which was subsequently weaned to 40 units per hour. However, she did not receive glucagon infusion as part of her treatment.

Post extubation, she did demonstrate a brief period of cognitive impairment but later improved, scoring 28/30 on her Mini-Mental Status Examination (MMSE) before her ICU discharge. She continued to make excellent recovery and was discharged to the medical wards for further medical and psychiatric evaluation.

Discussion

Propranolol poisoning causes severe cardiorespiratory collapse and remains a complex condition to manage. Cases in Australia continue to occur and pose many challenges to treating physicians. Despite conventional treatment, refractory cases often fail to improve solely with this. In such instances, early E-CPR and ECMO have been shown to improve patients' mortality rates [8].

Briefly, there are mainly two ECMO variations; VA-ECMO (Veno-Arterial ECMO), often used to provide cardiopulmonary support, involves inserting two large catheters into a large venous and arterial vessel. Blood is then drawn from the venous cannula into an extracorporeal pump that incorporates fresh gas within it. It is then delivered via the arterial cannula into the arterial circulation. VA-ECMO is almost exclusively used in severe cardiorespiratory failure.

The alternative is VV-ECMO (Veno-Venous ECMO) which requires a functioning heart to pump oxygenated blood throughout the body [9]. Often it is employed in fulminant respiratory failure, providing rest to the lungs while it continues to oxygenate the systemic circulation.

The utility of ECPR and ECMO in severe propranolol poisoning has been documented in several international case reports [10]. However, in Australia over the last ten years, our literature search has shown the lack of a single documented case of either E-CPR or ECMO used in severe refractory propranolol poisoning.

The '*dilemma*' of standard therapy

Before the ECLS era, the treatment for propranolol poisoning had been well established. The primary treatment involved hyperinsulinemic-euglycemic infusion and glucagon in providing adequate inotropy support to the affected heart. In addition, IV calcium supplementation ensured adequate calcium for inotropy, sodium bicarbonate to antagonize the Na^+ channel blockade [11], and IV lipid emulsion creating a '*lipid sink*' to shift the lipophilic drug from systemic circulation [12]. Hemodialysis was noted to be ineffective in propranolol toxidromes.

However, in severe refractory cases, these treatment modalities have been noted to be inadequate [13]. Often, catastrophic cases are un-survivable, with a few that are left vegetated due to hypoxic brain injury from prolonged CPR.

The role of E-CPR and ECLS

Extracorporeal life support allows for the continuing perfusion and oxygenation of vital tissues even in severe hemodynamic compromise. Once established, this temporizing artificial circulatory system provides the required amount of time for the protein-bound drug to be metabolized and excreted.

The timing of initiating ECLS is crucial. An earlier established circulation lessens the hypoxic impact on vital organs. Hence, E-CPR and ECMO offer excellent bridging options in such toxidromes [14].

However, ECLS poses several challenges [15]. Firstly, expert proceduralists must perform the cannulation, which becomes more complex under E-CPR. Also, echocardiographic guidance with Trans-Oesophageal Echocardiography (TOE) must be expertly performed to confirm catheter placement.

Clinical experience is vital when managing complex ECMO patients and logistically, mobilizing ECMO patients carries significant risk with possible adverse outcomes.

Despite these challenges, overall, ECLS remains a relatively safe and efficient therapeutic option. Although previous data have demonstrated low success rates of survival to hospital discharge [16], in this particular case, ECPR and ECMO provided the salvage therapy necessary to survive the catastrophic toxidrome.

In conclusion, ECPR and ECMO should be initiated early in patients with life-threatening cardiotoxicity secondary to acute propranolol toxicity. In addition, clinical vigilance is necessary to identify this toxidrome, start treatment with high-dose insulin and glucagon infusion, and attempt to transfer patients to a tertiary hospital with ECLS services. On the contrary, in ECLS-ready hospitals, continual excellence in service must be maintained, with fast access times and rapid initiation to ensure overall patients survival.

References

1. Scarth E, Smith S. Propranolol. Drugs in Anaesthesia and Intensive Care, 5th Ed. Oxford University Press, United Kingdom. 2016. p. 330-31.
2. Irwin SR, Lilly MC. Beta-blocker poisoning. Irwin and Rippe Intensive Care Medicine, 8th Ed. Wolters Kluwer, Philadelphia. 2018. p. 1015-9.
3. Brunton LL, Hilal-Dandan R. Propranolol. Goodman & Gilman's The Pharmacological Basis of Therapeutics 13th Ed. McGraw Hill Education, United States of America. 2018. p. 215.
4. Shand DG. Pharmacokinetic properties of the adrenergic receptor blocking drugs. Drugs. 1974;7(1):39-47.
5. Chen L-W, Mao DR, Chen Y-S. Extracorporeal life support: The final 'antidote' for massive propranolol overdose. Hong Kong J Emerg Med. 2019;26(2):118-23.
6. Vučinić S, Joksović D, Jovanović D, Vučinić Ž, Todorović V. Factors influencing the severity of the clinical picture and the outcome of beta-blocker poisoning. Military Med Rev. 2000;57(6):619-23.
7. Von Lewinski D, Bruns S, Walther S, Kögler H, Pieske B. Insulin causes [Ca2+]i-dependent and [Ca2+]i-independent positive inotropic effects in failing human myocardium. Circulation. 2005;111(20):2588-95.
8. Escajeda JT, Katz KD, Rittenberger JC. Successful treatment of metoprolol-induced cardiac arrest with high-dose insulin, lipid emulsion, and ECMO. Am J Emerg Med. 2015;33(8):1111.
9. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: A systematic review. J Toxicol Clin Toxicol. 2003;41(5):595-602.
10. Kolcz J, Pietrzyk J, Januszewska K, Procelewska M, Mroczek T, Malec E. Extracorporeal life support in severe propranolol and verapamil intoxication. J Intensive Care Med. 2007;22(6):381-5.
11. Shanker UR, Webb J, Kotze A. Sodium bicarbonate to treat massive beta-blocker overdose. Emerg Med J. 2003;20(4):393.
12. Jovic-Stosic J, Gligic B, Putic V, Brajkovic G, Spasic R. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: A case report. Clin Toxicol (Phila). 2011;49(5):426-30.

13. Love JN, Howell JM, Newsome JT, Skibbie DF, Dickerson LW, Henderson KJ. The effect of sodium bicarbonate on propranolol-induced cardiovascular toxicity in a canine model. J Toxicol Clin Toxicol. 2000;38(4):421-8.

14. Daubin C, Lehoux P, Ivascau C. Extracorporeal life support in severe drug intoxication: A retrospective cohort study of seventeen cases. Crit Care. 2009;13(4):R138.

15. Rupprecht L, Lunz D, Philipp A, Lubnow M, Schmid C. Pitfalls in percutaneous ECMO cannulation. Heart Lung Vessel. 2015;7(4):320-6.

16. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. Resuscitation. 2017;112:34-40.