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Case Report

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Case Report: Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) as a Bridge Therapy for Tricyclic Antidepressants Toxicity

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ABSTRACT

Background: Tricyclic antidepressants (TCAs) are neuropsychiatric agents ideal for overdose cardiac toxicity, which manifested as refractory hypotension, dysrhythmias, cardiogenic shock and cardiac arrest. In this situation, veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO), as the last resort, may be life saving.

Case Report: We report a 26- year-old female patient with a history TCAs toxicity presented with cardiac arrest. Return of spontaneous circulation (ROSC) achieved after 5 cycles of CPR. TCA was positive in urine then came later positive in serum sample (> 1000 ng/ml). Bedside echocardiography revealed severe cardiomyopathy (ejection fraction 35%) and global hyperkinesia. The decision was extracorporeal life support (ECLS) and veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO) was instituted. After 24 hours of hemodynamic stabilization on the VA-ECMO, inotropic support started tapering, QRS duration was normalized, the patient tolerated low pump flow 1,5 l/min and even sedation vacation. ECMO was weaned off on the 6th day and the patient was extubated on the 9th day of ICU admission.

Discussion: Management of our patient initially involved basic resuscitation with airway protection, good hydration, CPR upon cardiac arrest and post-ROSC support of circulation up to initiation of VA ECMO. Few case reports were published documenting VA ECMO indication in TCA toxicity patients. The most distingusible points are that, all patients were successfully weaned off from the VA ECMO and early ECMO intervention since TCA ingestion was crucial.

Conclusion: VA ECMO is a therapeutic option as a bridge for recovery in TCA and induced cardiac toxicity.

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Abbreviations
IV: Intravenous
IVI: Intravenous Infusion
ER: Emergency Room
MAP: Mean Arterial Blood Pressure
ROSC: Return of Spontaneous Circulation
BNP: A B-Type Natriuretic Peptide (BNP)

Introduction

Tricyclic antidepressants are a class of medications that has many indications such as depression, migraine, headache prophylaxis, neuropathic pain, obsessive-compulsive disorder and nocturnal enuresis. Because of their neuropsychiatric indications, they are accessible for suicidal attempt and overdose in patients with major depression.

TCAs are ideal agents for overdose toxicity; Long elimination half-life (25 to 81 hours), large volume of distribution (10-20 L/kg), highly bound to plasma protein (up to 95%), high lipid solubility, narrow therapeutic index (200-300 ng/mL), non-dialyzable and hemodialysis is ineffective. Major toxicity and death is associated with concentrations above 1000 ng/ml [1-3].

Table 1: Mechanisms of TCA induced cardiac toxicity [4].

Possible Mechanism	Its Effect
Blockade of Fast Sodium Channels in Myocardial Cells.	• Prolongation of Phase "0" of the Myocardial Action Potential. • QRS Prolongation. • Bradycardia.
Blockade of Potassium Channel.	• QT prolongation. • Torsades de Pointes.
A quinidine-Like Toxic Effect.	• Myocardial Depression. • Hypotension.
Blockade of Peripheral Alpha-Adrenergic Receptors.	• Hypotension.

The cardiac toxicity of TCAs is a challenge to treat being manifested as refractory hypotension, dysrhythmias, cardiogenic shock (not responding to IV fluid, sodium bicarb and inotropic support) and cardiac arrest. In this situation, veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO), as the last resort, may be life saving. Specifically, VA-ECMO is effective in critically ill poisoned patients who do not respond to conventional therapies [5].

Case Presentation

A 26- year-old female patient with a history of mild depressive disorder and generalized anxiety disorder, was found by her family unconscious. By history taking, she was on polydrug antidepressant medications including Venlafaxine, Agomelatine, Brexpiprazole and Paroxetine. No witnessed convulsions. Upon ER admission, Glasgow coma scale was 5/15, blood pressure (65/40, MAP 48) and heart rate 87 b/min. Arterial blood gases revealed hypercapnia respiratory acidosis pH 6.8, PaCO2 159.7 mm Hg, so immediately intubated and mechanically ventilated. Norepinephrine intravenous infusion was initiated with ongoing intravenous fluid bolus. TCA was positive in urine then came later positive in serum sample (> 1000 ng/ml). The level of possible co-investments (opioids, benzodiazepines, paracetamol, and ethanol) were negative.

She had a cardiac arrest, 5 cycles of CPR conducted according to the ACLS, then ROSC was achieved (2DC shocks were given because of pulseless V-tach). Post-resuscitation, she was hemodynamically unstable, not responding to Intravenous fluid bolus, escalation of inotropes and sodium bicarb 2 mEq/kg bolus.

Nasogastric lavage done and subsequently, activated charcoal was administrated. Electrocardiogram before arrest shows prolonged (corrected QT) interval (512 ms), QRS duration (140 ms), left axis deviation with right bundle and no ischemic changes. R wave was of 6 mm and R/S ratio was 5:1 in a VR (Figure 1 & 2).

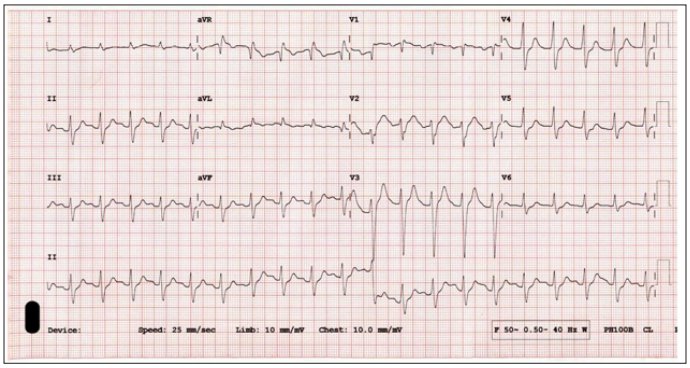

Figure 1

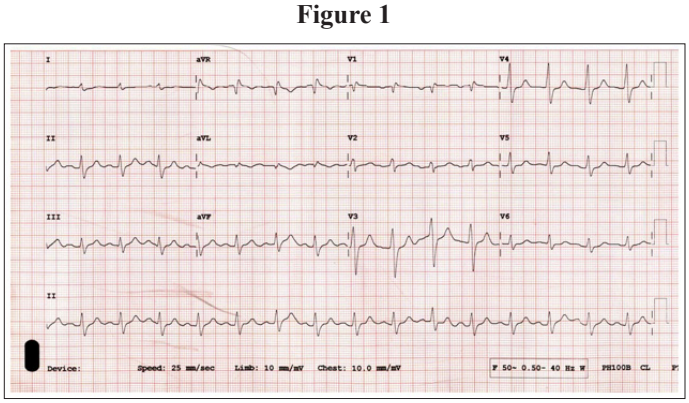

Figure 2

BNP was slightly elevated and troponin was normal. Bedside echocardiography revealed severe cardiomyopathy (ejection fraction 35%) and global hypokinesia.After consulting the ECMO team, the decision was extracorporeal life support (ECLS) and VA-ECMO was instituted in cath-Lab.

The ECMO configuration was as following: No 19 Inflow cannula was inserted percutaneously through the right femoral artery and connected to the inflow connection on the ECMO machine. A No 21 venous cannula was inserted percutaneously through the femoral route on the right side and connected to the outflow connection on the ECMO machine. Circuit was established and ECMO run started.

For retrograde perfusion, cannula was introduced into the distal femoral artery and connected to the arterial limb of the ECMO circuit. The initial pump flow was 3.5 litres/minute.

The patient was shifted to the Intensive Care Unit where kept deeply sedated and ventilated with lung protective strategy. Chest Radiographic Examination showed pulmonary oedema which responded to loop diuretics. Sodium bicarb administration was continued as 50 mEq every 8hours. After 24 hours of hemodynamic stabilization on the VA-ECMO, inotropic support started tapering down with discontinuation of dobutamine, vasopressin and norepinephrine in that sequence. QRS duration was normalized whereas QT interval was still prolonged (498 ms). The patient tolerated low pump flow 1,5 l/min and even sedation vacation. Meanwhile serial follow-up echocardiography confirmed gradual improve in myocardial contractility up to ejection fraction 50%. Therefore, ECMO was weaned off on the 6th day and the patient was extubated, after regaining full consciousness, on the 9th day of ICU admission. QT interval was normalized after 7 days of TCA ingestion.

During her course on the VA ECMO, the patient developed right leg swelling with weak peripheral pulsation. Doppler Ultrasound showed right ilio-femoral vein and inferior vena caval thrombosis which was confirmed later by Computerized Tomography lower limb angiography. Right femoral embolectomy with repair of right femoral artery with a Jotec graft was done during the same set of VA ECMO decannulation in the Cath-lab.

Development of extensive venous thrombosis in a patient on VA ECMO despite of non-stopped continuous heparin IVI would necessitate investigation. Hence, all thrombophilia profile was sent and revealed thrombotic antiphospholipid syndrome with positive anti beta 2 glycoprotein IgG for which she discharged on oral anticoagulant, warfarin, with target International Normalised Ratio 2-3.

Discussion and Conclusion

Management of our patient initially involved basic resuscitation with airway protection, good hydration, CPR upon cardiac arrest and post-ROSC support of circulation up to initiation of VA ECMO.

Activated charcoal and Sodium bicarbonate were empirically given. Activated charcoal is effective up to 2 hours' post-ingestion and should be given after securing the airway. Although Sodium bicarbonate was administrated to compensate acidosis and hemodynamic instability, it also was beneficial as an antidote for TCA toxicity. Indeed, QT and QRS prolongation raised the suspicion of TCA toxicity and supported the rationale for sodium

bicarbonate even before the result of toxicology screen.

Venlafaxine toxicity can not be excluded in our patient. Its toxicity is less than that of TCAs, but significantly higher than the selective serotonin reuptake inhibitors (SSRIs) [6]. Venlafaxine has one of the highest risks of QT prolongation in overdose, with the associated risk of torsades de pointes, reversible cardiomyopathy and sudden cardiac arrest [7].

VA ECMO is a therapeutic option as a bridge for recovery in TCA and Venlafaxine induced cardiac toxicity. Since 1993, Goodwin DA and colleagues reported a case of near fatal TCA overdose that failed to respond to standard therapy but was resuscitated using extracorporeal circulation [8]. Henceforth, few case reports were published documenting VA ECMO indication in TCA toxicity patients (table 2). The most distingusible point is that, all patients were successfully weaned off from the VA ECMO that indicates its effectiveness in treating such difficult cases. Early ECMO intervention since TCA ingestion may also be crucial. VA ECMO would gurantee adequate tissue perfusion and buys time until TCA fades out of the body. Normalization of QT interval and QRS duration may connote to the proper time to start VA ECMO weaning.

Table 2: Difference between Some Published Case Reports and Our Case

	Ingested Agent	The duration of ECMO (hours)
This case	Venlafaxine	144
Goodwin DA et al., 1993 [8].	Desipramine	60
Williams JM et al., 1994 [10].	Imipramine	7
Kobayashi K et al., 2011 [11].	Nortriptyline	14
Kejiri et al., 2021 [12].	Amitriptyline	27

Theoretically, VA ECMO may affect the pharmacokinetics of TCA by Several ways:

- The ECMO circuit may increase the volume of distribution especially with the introduction of priming solutions that may dilute the plasma proteins increasing the un-bound part of the drug, to be available for hepatic metabolism [9].
- The membrane oxygenator and polyvinyl chloride (PVC) tubing comprise a large surface area for potential drug sequestration, which may lead to drug loss over time, particularly for lipophilic drugs [9].
- Maintaining hepatic blood flow in haemodynaically unstable patient may facilitate hepatic clearance of TCAs medications.

Further studies may be required to explain the possible interactions between VA ECMO and TCA pharmacokinetics.

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