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Severe Verapamil Intoxication Requiring Plasmapheresis: A Case Report

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Abstract

Objective: Despite lack of evidence, plasmapheresis in severe verapamil intoxication may be indicated.

Case Presentation: We present the case of a 44-year old man with life-threatening verapamil intoxication as a suicidal attempt. He was admitted to the emergency department with general malaise, dyspnea and abdominal pain. Despite supportive therapy, he became hypotensive and unresponsive. He was transferred to the intensive care unit for urgent plasmapheresis.

Conclusion: Although scattered evidence suggests a possible benefit of plasmapheresis for severe verapamil intoxication, the EXTRIP workgroup recommends against.

Keywords: Verapamil, Intoxication, Plasmapheresis, Calcium channel blocker

Introduction

Verapamil is a non-dihydropyridine calcium channel blocker used in patients with arterial hypertension, supraventricular arrhythmias or migraine. It blocks rapid calcium influx into the cardiac myocytes of the conduction system and smooth muscle cells of the vasculature, resulting in decreased myocardial contractility, prolonged conduction time and peripheral vascular relaxation [1]. It is a phenylalkylamine-derived calcium-channel blocking agent. Chemically it is a basic and highly hydrophobic compound. More than 90% of verapamil is absorbed when given orally, but due to high first-pass metabolism, its bioavailability is less (10-35%). It is 90% bound to plasma proteins and takes 1-2 hours to reach peak plasma concentration after oral administration. It is metabolized in the liver by CYP450. Overall 70% is excreted in the urine and 16% in feces. Blockage of L-type voltage-gated calcium channels, which is selective in non-dihydropyridines, will decrease the release of insulin from the pancreatic beta-cells and hence reduce the glucose uptake by peripheral tissues (insulin resistance) [2].

Verapamil intoxication is a potential life-threatening condition, which requires urgenttreatment. Mortality rates vary between 0.3 and 25% [3]. Cardiovascular dysfunction is the main cause for hemodynamic instability, characterized by hypotension, bradycardia, (brady) dysrhythmias or intraventricular conduction delay [2]. Treatment of patients with verapamil intoxication is supportive. Bradycardia can be treated with atropine or isoprenaline infusion and hypotension with crystalloid infusion and calcium boluses. Gastrointestinal decontamination (activated charcoal and whole bowel irrigation) is recommended in those with large ingestions and in the early phase of presentation. High dose insulin euglycemic therapy is approved. There is a lack of evidence in literature to recommend intravenous lipid emulsion in routine therapy. Because verapamil is highly protein bound, extracorporeal removal by hemodialysis is not effective [3]. In case of persistent bradycardia or hypotension, transvenous or transcutaneous pacing can be performed. Extracorporeal membrane oxygenation (ECMO) is useful for patients presenting with cardiogenic shock [3].

We present a patient with severe verapamil intoxication unresponsive to supportive therapy.

Case Description

A 44-year-old man with a medical history of arterial hypertension, cluster headache, alcohol abuse and depression was admitted to the emergency department 36 hours after ingestion of sustained-release (SR) 4800 mg verapamil as a suicide attempt. He presented with general malaise, dyspnea and abdominal pain.

A clinical examination revealed hypotension (86/72 mmHg) and bradycardia (60 beats/min). First he was alert and cooperative, but slightly he became more unresponsive. Toxicologic screening for other agents was negative. ECG findings (Fig. 1) revealed atrial fibrillation with a relatively slow ventricular response. Biochemical evaluation showed a slight leukocytosis (31,700 µg/L), mild hyponatremia (124 mmol/L), mild hyperkalemia (5.3 mmol/L), mild hypocalcemia (1.16 mmol/L) and creatinine of 5.17 mg/dL. He was normoglycemic (134 mg/dL). Blood levels of lithium and paracetamol were low. Arterial blood gas analysis showed a metabolic acidosis with pH of 7.29, normal pCO_2 (pCO_2 39 mmHg) and low pO_2 (44 mmHg), bicarbonate of 15.5 mmol/L, lactate of 8.9 mg/dL.

Supportive therapy was initiated, except for activated charcoal

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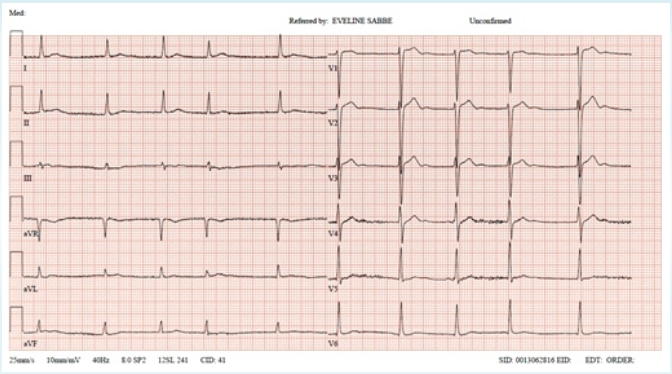

Figure 1: ECG

T (min)	Verapamil plasma concentration (µg/L)	Norverapamil plasma concentration (µg/L)
0	1541	1211
30	952	804
60	846	746
90	808	739
120 (end plasmapheresis)	750	693
140 (filtrate)	738	616

Figure 2: Plasmapheresis

because of the tardive presentation. However, additional interventions were needed to stabilize this life threatening condition. A bolus of intravenous Intralipid 20% emulsion (100 ml) was given, although without direct clinical effect. A pharmacobezoar was not detected on gastro-esophageal endoscopy. Consequently, he was admitted to the Intensive Care Unit (ICU) for urgent plasmapheresis and hemodialysis.

In retrospect, the verapamil plasma concentration at the start of plasmapheresis was 1541 µg/L. The hemodynamic condition stabilized quickly during plasmapheresis. 3.6 mg was removed over a time period of 2 hours (removed plasma volume 4200 ml). This led to stabilization of the clinical situation.

Discussion

In our case, a patient with a clinical relevant and life-threatening verapamil intoxication was treated with plasmapheresis because supportive measures were insufficient to stabilize the patient after admission. The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup recommends against using extracorporeal methods to enhance the elimination of verapamil in patients with severe poisoning [3]. However, it may be feasible in clinical situations where standard supportive therapy is insufficient. A percentage of CCB removal lower than 1% of the ingested dose or total body stores in 6 hours is considered insignificant.

There is an increasing interest in use of intravenous lipid emulsion to treat life-threatening toxicity from several lipophilic drugs. There are favorable case reports in using Intralipid in verapamil intoxications, especially in children. There are also reports of improved hemodynamic parameters and increased survival in animal models of verapamil toxicity when given intravenous lipids [4-6]. The Lipid Emulsion Workgroup concluded that there is insufficient evidence to recommend lipid emulsion therapy in the routine management of CCB poisoning [7].

In CCB intoxication, hyperglycemia is correlated to the severity of non-dihydropyridine poisoning. High-dose insulin (bolus of 1 unit/kg followed by 0.5-2.0 units/kg/h) is associated with improved hemodynamic parameters and lower mortality, at the risks of hypoglycemia and hypokalemia. High-dose insulin has a positive inotropic effect and is supported by some degree of evidence but the evidence remains of low quality [8-9].

Gastrointestinal decontamination with activated charcoal belongs to the standard care of intoxication, but was not implemented in this case because of late presentation. Whole bowel irrigation can be useful, especially with modified release preparations but wasn't undertaken in this patient because of the risk of aspiration [10-12].

Adjunct treatment with a vasopressor (noradrenaline) resulted only in mild amelioration. Very high doses of vasopressors may be necessary to counteract the vasodilatory effect of verapamil.

Supportive measures seemed insufficient to stabilize the patient after admission in ICU. A high morbidity and mortality is reported following massive CCB poisoning. Higher blood concentrations of CCB are associated with worse outcomes. In a study of 65 verapamil-toxic patients, the only independent risk factor associated with mortality was the verapamil concentration with a cut-off point determined to be 2273 ùg/L [13].

Because of this unstable condition and the high dose of a slow release form that was taken, additional elimination was attempted using plasmapheresis. In total a volume of 4200 ml plasma was eliminated (containing 3099 microgram of verapamil and 2587 microgram of norverapamil).

The extracorporeal treatments in poisoning (EXTRIP) workgroup recommends against using extracorporeal methods to enhance the elimination of verapamil in patients with severe poisoning. Verapamil is highly protein bound and is non dialyzable. It has a large volume of distribution and high endogenous clearances which means that any type of ECTR will theoretically be inconsequential at enhancing the elimination of verapamil. In overdose, protein binding and endogenous clearance (400-600 ml/min) remains relatively unchanged.

The fall of CCB concentrations may be solely accounted for by the endogenous clearance.

In our case the patient stabilized during the plasma exchange therapy. A potential indirect toxicodynamic effect from ECTR could be considered, as some studies suggested an improvement in hemodynamics during ECTR (especially liver support devices). Postulates for this effect include extracorporeal removal of nitric oxide and pro-inflammatory vasoactive cytokines, as well as support of liver function.

Conclusion

We present a case report of a verapamil intoxication in need for additional, less conventional therapy, i.e. plasmapheresis. Although

scattered evidence suggests a possible benefit, the EXTRIP workgroup recommends against.

Current evidence suggests against the use of extracorporeal methods in general and plasmapheresis specifically. However, a beneficial effect is suggestive. In conclusion, plasmapheresis should be considered as an additional treatment option in verapamil intoxication if standard supportive therapy is insufficient to stabilize hemodynamics.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the Journal. The patient understands that his/her name and initials will not be published, and due efforts will be made to conceal his/her identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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