CASE REPORTS

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Successful usage of intravenous lipid emulsion in treatment of acute verapamil poisoning – A case report

Uspešna primena intravenskih emulzija masti u terapiji akutnog trovanja verapamilom

Gordana Vuković Ercegović*, Nataša Perković Vukčević*, Snežana Djordjević*†, Zoran Šegrt†, Olivera Potrebić*, Snežana R. Janković‡, Jasmina Jović Stošić*†, Nadica Marinković†§

***National Poison Control Center, ‡Institute for Scientific Information, §Institute of Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia**

Abstract

Introduction. During the last few years, intravenous lipid emulsions have been effectively used in treatment of acute poisonings with lipophilic substances, including verapamil. **Case report.** A 37-year-old women presented 1 hour after ingestion of 2.8 g verapamil with hypotension and complete heart block. Because of the applied standard therapy failure and further patients impairment, Intralipid® 20% was used. Sinus rhythm was restored, arterial blood pressure increased and verapamile concentrations, both total and free decreased. **Conclusion.** Intravenous lipid emulsion can be important in treatment of severe acute intoxication and cardiotoxicity caused by verapamil.

Key words:
poisoning; suicide; verapamil; calcium channel blockers; heart block; fat emulsions, intravenous; treatment outcome.

Apstrakt

Uvod. Poslednjih godina intravenske emulzije masti uspešno se koriste u terapiji akutnih trovanja lipofilnim supstancama, uključujući i verapamil. **Prikaz bolesnika.** Prikazana je 37-godišnja pacijentkinja primljena jedan sat nakon ingestije 2,8 g verapamila. Na prijemu je bila hipotenzivna, sa kompletnim srčanim blokom. Zbog izostanka efekta primenjene standardne terapije i daljeg pogoršanja stanja pacijentkinje primenjen je Intralipid® 20%, nakon čega je uspostavljen sinusni ritam. Zabeležen je porast arterijskog pritiska, uz smanjenje koncentracije verapamila, kako ukupnog, tako i slobodne frakcije leka. **Zaključak.** Intravenske emulzije masti mogu zauzeti važno mesto u terapiji teške akutne intoksikacije i kardiotoksičnosti uzrokovane verapamilom.

Ključne reči:
trovanje; samoubistvo; verapamil; kalcijum, blokatori; srce, blok; masne emulzije, intravenske; lečenje, ishod.

Introduction

Verapamil is a phenylalkylamine calcium channel blocker used in treatment of angina pectoris, arrhythmia and arterial hypertension. Acute poisonings with this agent are not frequent, but can be severe with high mortality which can be predicted by serum verapamil concentration 1. Clinical manifestations include rapid development of hypotension, bradycardia or other types of dysrhythmias and cardiac conduction abnormalities. Severity of clinical manifestations depends on ingested doses, drug formulation and patient's comorbidity. Toxicity development may be delayed when sustained release tablets are ingested.

Standard treatment protocols include gastrointestinal decontamination, administration of fluids, atropine, calcium, glucagon, inotropic agents, hyperinsulinemia/euglycaemia protocol, temporary pacemaker insertion and supportive measures 2. Very often, cardiocirculatory shock remains refractory to applied antidote, inotropic and vasopressive therapy.

According to the above mentioned, definition and adoption of new and more successful treatment protocols are required.

Correspondence to: Gordana Vuković Ercegović, National Poison Control Center, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: gogavukerc@yahoo.com

During the last years, intravenous lipid emulsions (ILE) have been effectively used in treatment of acute poisonings with lipophilic substances, including verapamil [3]. We presented a case of severe verapamil intoxication successfully treated with ILE. Early administration of therapy led to fast and complete recovery and decrease of serum verapamil level.

Case report

A 37-year-old woman, with a medical history of psychosis and palpitations, presented after 1 hour of ingestion of 2.8 g verapamil in a suicide attempt. On admission the patient was alert, oriented, and eupnoic. The patient was hypotensive with blood pressure of 75/45 mmHg, heart rate was 65/min and oxygen saturation 97%. An electrocardiography (ECG) revealed complete heart block with widened QRS complex and frequent multifocal ventricular extrasystoles (Figure 1).

The initial therapy included isotonic fluids, glucagon (total dose of 10 mg) and calcium chloride (total dose of 1 g), and dopamine. One hour after starting the treatment the patients' condition deteriorated. The patient was somnolent, pale and more hypotensive with blood pressure of 70/30 mmHg. Intralipid® 20% (20% *iv* fat emulsion), 100 mL in *iv* bolus followed by continuous infusion of 400 mL over 30 min and additional 500 mL over the next 1 h was given. Approximately 45 min after starting with Inralipid®, sinus rhythm was restored and arterial blood pressure increased to 105/60 mmHg. The patient remained hemodynamically stable and dopamine infusion discontinued after six hours. ECG showed sinus rhythm with first degree AV block (Figure 2). On the day 3 ECG was normal.

Laboratory tests on arrival showed glucose level of 8.4 mmol/L (normal range 4.1–5.9 mmol/L) and blood urea nitrogen 1.7 mmol/L (normal range 2.5–7.5 mmol/L). Other initial laboratory investigations, comprising complete blood count, electrolytes, renal and liver function tests were in reference ranges and remained so during hospitalization.

The treatment completed without any complications. The patient was discharged on the day 6 and transferred to psychiatric hospital.

Determination of verapamil in serum samples was performed by high performance liquid chromatography with photo diode array detection (HPLC-PDA). After applying Intralipid® the lipid phase was removed by ultracentrifugation of sample on 0ºC and 13,500 rpm for 10 min. Lipid volume was determined by the difference in total serum volume with and after removing lipid phase. Verapamil in lipid phase was calculated as a difference between its quantity in the lipid serum and the serum after removing the lipid phase.

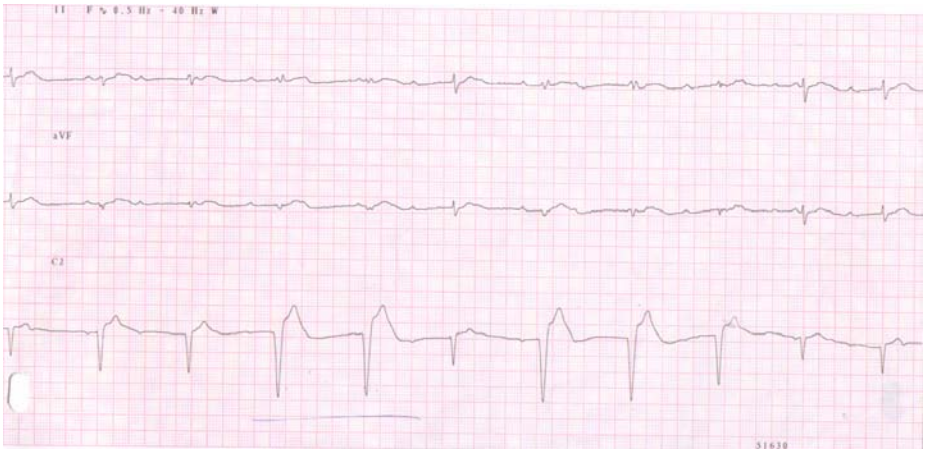

Fig. 1 – Electrocardiographic changes in the patient acutely poisoned by verapamil, noted before Intralipid® 20% administration, showed complete heart block with multifocal ventricular extrasystoles.

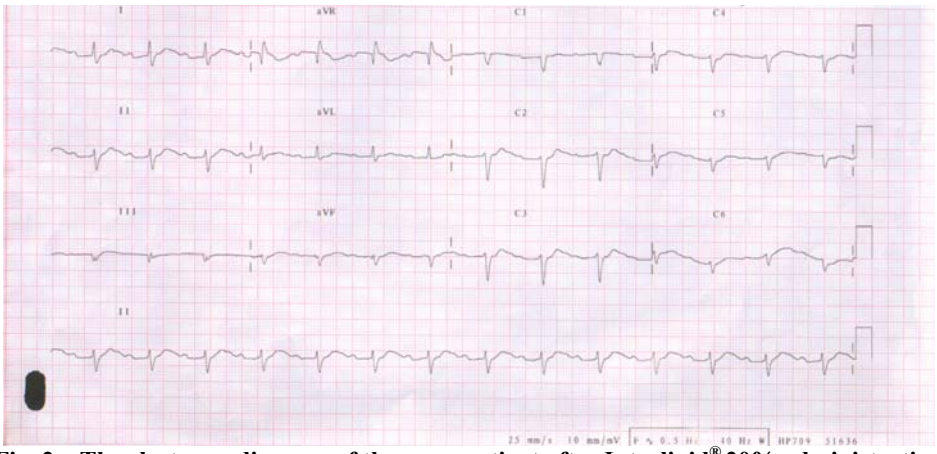

Fig. 2 – The electrocardiogram of the same patient after Intralipid® 20% administration showed sinus rhythm with first degree AV block.

The serum level of verapamil on admission was 2.2 mg/L and metabolites were positive (verapamil therapeutic values range 0.02–0.25 mg/L) [4]. Six hours after Intralipid® 20% administration, the total verapamil level was 1.04 mg/L, the level after removing lipid phase was 0.95 mg/L and the calculated level of verapamile in lipid phase was 11.34 mg/L.

Discussion

ILE have been used in parenteral nutrition for the last 50 years [5]. Over the last decade the use of ILE as antidote has opened new era in clinical toxicology. At the beginning, it has been recommended for the treatment of circulatory collapse and cardiac arrest due to local anaesthetics toxicity [6]. For these cases current dosage regimen is recommended by the Association of Anaesthetists of Great Britain and Ireland. The starting dose is *iv* bolus of Intralipid® 20% 1.5 mL/kg over 1 min with the subsequent 15 mL/kg/h. Bolus doses can be repeated and rate of infusion can be increased up to max 12 mL/kg [7]. There are many dilemmas about indications and dosage in the case of other liposoluble agents toxicity. The number of published case reports and animal studies that show effectiveness of ILE to reverse ECG changes, hemodynamic and neurological parameters in poisoning by lipophilic agents including verapamil, is increasing [3]. The mechanism of action and effectiveness of ILE in acute poisoning by lipophilic agents is basically explained by the 'lipid sink' theory. Lipid intravascular compartment, that is created, pulls lipophilic substances from the tissue and site of action (myocytes, brain) due to high lipid solubility and the established concentration gradient. This shift results in decreasing the free fraction substance concentration and clinical improvement [6, 8]. Increasing intracellular fatty acid and providing energy substrate for myocytes, cardioprotective effect, direct cardiotonic effect and activating calcium channels are some of the other mechanisms that contribute to efficacy of ILE [8].

In an animal model of severe verapamil toxicity it is demonstrated that ILE significantly prolong survival time, prevent the development of bradycardia, increase median lethal dose of the drug and increase mean arterial pressure (MAP) [9, 10].

Effectiveness of Intralipid® in acute verapamil poisoning has been confirmed in case reports [11–13]. The first case of a successful lipid rescue of verapamil poisoning was published by Young at al. [11] in 2009. A patient ingested 13 g of sustained released tablets of verapamil. He had refractory hypotension and junctional bradycardia. Intralipid® 20% was used in a dose of 100 mL over 20 min followed by infusion at 0.5 mL/kg/h for the next 23 h. During the first hour, systolic blood pressure increased and the patient was stabilized. In the report there were no data about ECG changes reversal rapidity. Total serum concentrations of verapamil and norverapamil, measured at 20 h and 36 h after ingestion were 0.99/1.11 μmol/L and 0.62/0.91 μmol/L, respectively.

French at al. [12] demonstrated reducing serum verapamil concentration after removing lipid phase and increasing in MAP associated with ILE administration. The ingested dose was 6.3 g, and the patient was hypotensive with complete heart block. Two 100 mL boluses of Intralipid® 20% followed by 500 mL *iv* infusion over 30 min were administered nineteen hours after ingestion. That resulted in improvement of patient's MAP and lowering of verapamil concentration in the serum. Deterioration of patient's condition with blood pressure decrease was reported 29 h after ingestion. Verapamil concentration increased and 100 mL bolus of Intralipid® was given. Again, hemodynamic improvement was followed by reducing verapamil concentration, but it remained elevated for the next few days. This can be explained by large amount of the sustained release formulation ingested and a lower Intralipid® 20% dose than necessary.

Clinical presentation and high serum verapamil concentration in the presented patient on admission, clearly indicated a serious cardiotoxicity. Failure of the applied standard therapy and further impairment of the patients' condition was the reason for ILE use. During administration, sinus rhythm was restored, arterial blood pressure increased and verapamil concentration, both, total and free serum fraction, decreased.

Efficiency of ILE is shown in acute poisoning with other Ca^{2+} - channel blockers, including diltiazem, nifedipine and amlodipine [8]. Knowing the similar characteristics of those drugs (liposolubility - partition coefficient and volume of distribution), such results are expected [14]. Yet, in assessment of ILE efficacy, we also should bear in mind the possibility of bias, because cases of successful treatment are mainly reported. There were rare case reports in which ILE was not effective. For example, in polydrug poisoning with prevailing effects of amlodipine or nifedipine, fatal outcomes due to respiratory and cardiocirculatory shock occurred despite the use of ILE [15]. However, other drugs probably contributed to the severity of poisoning in described cases and to the failure of ILE therapy.

Conclusion

Successful early usage of Intralipid® 20% in the presented patient, along with other cases in the literature supports lipid rescue treatment in severe verapamil-induced cardiotoxicity. In cases of severe acute intoxication and cardiotoxicity caused by verapamil we believe that there is no reason to delay the use of ILE.

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