



## Failure of intravenous lipid emulsion in treatment of cardiotoxicity caused by mixed overdose including dihydropyridine calcium channel blockers

Nedelotvornost intravenske emulzije masti u lečenju kardiotoksičnosti izazvane predoziranjem kombinacije lekova uključujući dihidropiridinske blokatore kalcijumovih kanala

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### Abstract

**Introduction.** Calcium channel blockers and beta-blockers are among the most frequently ingested cardiovascular drugs in self-poisoning causing significant mortality. Intravenous lipid emulsion (ILE) is reported as a potentially novel antidote for treatment of acute poisoning caused by some of these drugs. **Case report.** We presented two cases of poisoning with these drugs. The case 1, a 24-year-old woman ingested amlodipine, metformin and gliclazide for self-poisoning. She presented with tachycardia and hypotension. Laboratory analyses revealed hyperglycaemia and metabolic acidosis. Despite the treatment which included fluid resuscitation, vasopressors, intravenous calcium, glucagon and ILE, circulatory shock occurred. The patient died 10 hours after admission due to cardiac arrest refractory to cardiopulmonary resuscitation. The case 2, a 41-year old man, was found in a coma with empty packages of nifedipine, metoprolol and diazepam tablets. On admission vital signs included Glasgow Coma Scale (GCS) of 3, weak palpable pulses, undetectable blood pressure, and irregular breathing with oxygen saturation of 60%. An electrocardiography showed AV block (Mobitz II) with ventricular rate of 44/min with progression to third degree of AV block. In attempt to increase heart rate and blood pressure the following agents were administered: atropine boluses, normal saline with dopamine, glucagon, calcium chloride and ILE. Temporary transvenous pacemaker was placed, electrical capture was recorded, but without improvement in haemodynamics. Three hours after admission cardiac arrest happened and cardiopulmonary resuscitation was unsuccessful. **Conclusion.** Intravenous lipid emulsion may be ineffective in acute poisonings with amlodipine, nifedipine or metoprolol.

### Key words:

poisoning; suicide; calcium channel blockers; adrenergic beta-antagonists; heart arrest; fat emulsions, intravenous.

### Apstrakt

**Uvod.** Antagonisti kalcijumovih kanala i beta blokatori predstavljaju najčešće upotrebljavane kardiološke lekove prilikom samotrovanja koji prouzrokuju značajnu smrtnost. Intravenske emulzije masti (IEM) u poslednje vreme koriste se kao protivotrov u lečenju akutnih trovanja prouzrokovanih ovim lekovima. **Prikaz bolesnika.** Prikazali smo dva bolesnika otrovana ovim lekovima. Bolesnica, stara 24 godine, popila je tablete amlodipina, metformina i gliklazida u cilju samotrovanja. Klinička slika na prijemu uključivala je tahikardiju i hipotenziju, a laboratorijske analize hiperglikemiju i metaboličku acidozu. I pored terapije koja se sastojala od intravenske primene tečnosti, vazopresora, kalcijuma, glukagona i IEM, razvio se cirkulatorni šok. Deset časova nakon prijema došlo je do srčanog zastoja refrakternog na mere kardiopulmonalne resuscitacije. Drugi bolesnik, star 41 godinu, nađen je u komi sa ispražnjenim pakovanjima nifedipina, metoprolola i diazepam. Na prijemu, vrednost Glazgovske koma skale (GKS) iznosila je 3, postojao je slab palpabilan puls, krvni pritisak bio je nemerljiv, a disanje nepravilno sa zasićenjem kiseonikom od 60%. Na elektrokardiogramu registrovan je AV blok tipa Mobitz II sa komorskom frekvencijom od 44/min koji progredirao u AV blok III stepena. U terapiji su primenjivani bolusi atropina, fiziološki rastvor sa dopaminom, glukagon, kalcijum hlorid i ILE. Plasiran je privremeni pejsmejer čija se električna aktivnost registrovala, ali nije došlo do popravljavanja hemodinamskih parametara. Tri časa nakon prijema došlo je do srčanog zastoja refrakternog na terapiju. **Zaključak.** IEM mogu biti neefikasne u lečenju akutnih trovanja amlodipinom, nifedipinom i metoprololom.

### Ključne reči:

trovanje; samoubistvo; kalcijum, blokatori; adrenergički beta blokatori; srce, zastoj; masne emulzije, intravenske.

## Introduction

Calcium channel blockers (CCBs) and beta blockers are among the most frequently ingested cardiovascular drugs in self-poisoning<sup>1</sup>. Toxicity of CCBs is primarily a consequence of negative cardiac conduction and contractility properties, along with peripheral vasodilatory effects and is manifested as hypotension, bradycardia, heart block, and circulatory shock. Dihydropyridines (like nifedipine and amlodipine) tend to produce sinus tachycardia instead of bradycardia with fewer conduction disturbances than diltiazem and especially verapamil which tend to produce the most pronounced effects. Nevertheless, in severe overdoses these differences are less evident and all classes of CCBs are potentially fatal<sup>2,3</sup>.

Standard therapeutic modalities used in the management of CCB overdose include gastrointestinal decontamination, fluid resuscitation, vasopressor agents, atropine, intravenous calcium, glucagon, hyperinsulinemic euglycemia, and in some cases sodium bicarbonate or cardiac pacing<sup>4</sup>. Despite all these treatments, self-poisonings with CCBs continue to cause a significant mortality<sup>1</sup>. In recent years, intravenous lipid emulsion (ILE) is reported as a potentially novel antidote for overdoses of lipophilic substances including CCBs<sup>5,6</sup>. Published case reports of successful treatment in critically ill patients may suggest that ILE is more efficient and more powerful than it really is. Therefore, after some positive experience with ILE in treatment of cardiotoxicity in acute drug poisoning<sup>7-9</sup>, we reported two cases of poisoning with fatal outcome despite ILE administration.

## Case report

*Case 1.* A 24-year-old woman was brought to a local emergency department, approximately 2 hours after self-poisoning. The patient was able to provide history. She ingested 150 mg (30 tablets) of amlodipine, 10 g (20 tablets) of metformin, and 2.4 g (30 tablets) of gliclazide. There was no significant prior medical history. She was hypotensive with blood pressure of 80/40 mmHg. Gastric lavage was performed, intravenous glucose and dopamine were started and the patient was transferred to the hospital. She received 20 mL of calcium gluconate 10% during transportation.

On admission, 5 hours after drugs ingestion, the patient was alert, blood pressure was 70/30 mmHg despite dopamine infusion, and other vital signs were normal. A 12-lead ECG showed sinus rhythm, with a rate of 112/min and incomplete right bundle branch block. Laboratory results on presentation were normal except for glucose of 20 mmol/L. Arterial blood gases (ABG) showed pH 7.27, pCO<sub>2</sub> 28 mmHg, pO<sub>2</sub> 61 mmHg, lactates 4.9 mmol/L, acid-base excess (ABE) 13.1 mmol/L. Toxicological analysis of blood revealed metformin 6.32 mg/L, gliclazide 3.95 mg/L, and amlodipine 0.05 mg/L (HPLC-UV method).

The patient was admitted to the intensive care unit (ICU). She received additional intravenous fluids with glucagone (total dose of 15 mg) and calcium chloride (total dose of 2 g). Because she ingested hypoglycemic drugs, 10% glu-

cose was administered in continuous infusion and small dose of insulin was tapered to maintain glucose at upper normal level. Dopamine dose was gradually increased up to 40 µg/kg/min, but in a few hours blood pressure decreased to non measurable values. Lipid emulsion (Intralipid® 20%) was started 3 hours post-admission. The patient received 100 mL bolus followed by 400 mL in the next 20 minutes. It resulted in transient (during approximately 30 minutes) increase of blood pressure reaching maximum of 90/50 mmHg. Additional infusion of 500 ml 20% Intralipid® was given, but there was no significant improvement. All the time cardiac monitoring recorded sinus tachycardia with AV block grade I and ST depression of 3–4 mm. The patient remained hypotensive and without urine output for the next 10 hours when cardiac arrest refractory to cardiopulmonary resuscitation happened.

*Case 2.* A 41-year-old man was found by family members in a coma. They found empty packages of nifedipine, metoprolol and diazepam tablets which he was using in his hypertension therapy.

On admission the patient was in a coma (Glasgow coma score was 3), with weak palpable pulses, undetectable blood pressure, irregular breathing with respiratory rate of about 8 breaths *per* minute and oxygen saturation of 60%. An ECG showed second degree AV block (Mobitz II) with ventricular rate of 44/min.

The results of blood chemistry revealed glucose level of 16 mmol/L, while levels of electrolytes, blood urea nitrogen (BUN), creatinine, transaminases and creatine kinase were normal. Toxicological analysis of blood proved nifedipine in concentration of 0.62 mg/L, metoprolol 0.57 mg/L, and diazepam 1.04 mg/L (HPLC-UV method).

The patient was promptly intubated without medication and placed on mechanical ventilation. In attempt to increase heart rate and blood pressure the following agents were administered: atropine (in boluses), normal saline with dopamine, glucagon (12 mg, given as 3 mg boluses), calcium chloride (1g), intravenous lipid emulsion (500 ml of Intralipid® 20% solution). Despite these, the patient's systolic blood pressure remained in the range of 50–70 mmHg, and ECG monitoring showed worsening with third degree AV block. Temporary transvenous pacemaker was placed. Though electrical capture was recorded, there was no improvement in blood pressure. Three hours after admission cardiac arrest happened and cardiopulmonary resuscitation was unsuccessful.

## Discussion

Intravenous lipid emulsion is thought to act through several mechanisms including shifting of lipophilic drugs from tissue into circulation, providing energy for heart muscle from lipid acids, or enabling calcium influx into myocardium<sup>10</sup>. The first mentioned, so-called lipid sink mechanism is supported by experimental studies showing that ILE is effective in cases of certain lipophilic substances, especially local anesthetics<sup>11</sup>. However, ILE was not always superior to standard treatment protocols in attenuating toxicity of some

other drugs, including CBBs<sup>12</sup>. Though there is an emerging number of case reports suggesting benefit of lipid emulsion use in poisoned patients<sup>6</sup>, in order to gain more experience with different agents, we find it important also to present cases in which ILE was not effective.

The first case we reported was fatal overdose with amlodipine and oral antidiabetics (metformin and gliclazide). Refractory hypotension due to peripheral vasodilatation and tachycardia as a reflex cardiac response may be attributed largely to amlodipine<sup>13</sup>, though metformin may contribute to these effects<sup>14</sup>. The initial hyperglycemia despite hypoglycemics co-ingestion, is also suggestive of CBBs suppression of insulin release. Metabolic acidosis with border-line elevated lactate may be a consequence of reduced peripheral perfusion but metformin also may add to it<sup>15</sup>.

The patient did not respond to standard therapy. Because of gliclazide co-ingestion and the risk of prolonged hypoglycaemia<sup>16</sup>, hyperinsulinemic euglycemia treatment protocol was not tried. Due to the lipophilic nature of amlodipine, lipid emulsion rescue therapy was administered. Though benefits of ILE in critical patients ingested amlodipine has been presented in several reports<sup>17–20</sup> the only noticeable effect in our patient was transient, unsustainable increase of blood pressure.

The second case we presented was a fatal poisoning with combination of calcium channel blocker (nifedipine), beta blocker (metoprolol) and benzodiazepine (diazepam).

In this case, cardiotoxicity with third-degree AV block and circulatory shock may be attributed to synergic action of metoprolol and nifedipine. ILE may be not effective with less lipophilic beta blockers such as metoprolol compared with propranolol<sup>8, 21–23</sup>. However, in case of metoprolol-induced cardiac arrest refractory to standard treatment, combination of high-dose insulin, lipid emulsion and venoarterial extracorporeal membrane oxygenation was successful rescue therapy<sup>24</sup>. On the other side, ILE was not effective in reversal of metoprolol-induced hypotension in rabbit model<sup>25</sup>. The other cardiotoxic drug ingested by our patient, nifedipine, is relatively lipophilic and some benefit may be expected from ILE though experimental study in rats showed no significant difference in the haemodynamic parameters and mortality between groups receiving ILE or placebo<sup>26</sup>. In the presented case, there was no response at all, neither to medications, including ILE, nor to cardiac pacing.

### Conclusion

Reports on the beneficial effect of lipid emulsion in poisoning with different agents have accumulated in recent years. Though intravenous lipid emulsion may be life-saving treatment of poisonings with certain calcium channel blockers or beta blockers, like verapamil and propranolol, it may be ineffective in some other circumstances, including toxicity of amlodipine, nifedipine and metoprolol.

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