CASE REPORT

Lipid Rescue Therapy and High-Dose Insulin Euglycemic Therapy are Effective for Severe Refractory Calcium Channel Blocker Overdose: Case Report and Review of Literature

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Abstract

Background: High-Dose Insulin Euglycemic Therapy (HIET) and Lipid Rescue Therapy (LRT) are new alternative treatments for acute poisoning with calcium channel blockers. In this report a severely poisoned patient with verapamil and furosemide who was successfully treated with these two treatments is presented.
Case report: A 27-year-old woman was brought to "Mother Theresa" Clinical Center in Skopje with a history of consumption of 24 grams (100 pills) sustained-release verapamil and 4 grams (10 pills) furosemide. She was alert and oriented with 60/35 mmHg blood pressure (BP), her respiratory rate was 25 breaths/min and heart rate was 40 beats/min with first degree atrioventricular (AV) block on electrocardiogram (ECG). In the first 90 minutes, she received activated charcoal, 1 liter of 0.9% saline, 60 mL of calcium chloride ($CaCl_2$), 40 mg potassium and subsequently dopamine and 100 mg noradrenaline. However, there was no significant improvement in her hemodynamic status (BP = 70/50 mmHg) and she developed second degree AV block. Temporary pace maker was implanted. In the next one hour, the patient had stable vital signs, when she again became hypotensive (BP = 60/35 mmHg) with prolonged QRS complex (20 msec). During this period she was treated with epinephrine (9mg), atropine (2mg), isoprenalin, bicarbonate, $CaCl_2$ and intravenous fluid. Unsuccessful conventional treatments indicated administration of HIET and LRT. Three hours later, the BP was normalized (110/75mm) and 36 hours later, all ECG disturbances disappeared. She left the Clinic without any sequels, four days later.
Conclusion: LRT in addition to HIET are effective treatments for CCB overdose. LRT can be considered as a standard treatment for CCB overdose. Nevertheless, further investigations are necessary to establish the real value of these treatments.

Keywords: Calcium Channel Blockers; Intravenous Fat Emulsions; Poisoning; Verapamil

INTRODUCTION

Calcium channel blocker (CCB) overdose is emerging as one of the most common causes of prescription drug-related fatalities (1). The use of CCBs as an antihypertensive treatment is increasing worldwide (2,3), leading to a parallel increase in potential CCB overdoses. Calcium channel blockers and beta-blockers (BB) account for approximately 40% of cardiovascular drug exposures reported to the American Association of Poison Centers (1). However, these drugs are responsible for more than 65% of deaths from cardiovascular medications (4). Acute suicidal poisonings with CCBs are common in Macedonia, with more than 7.5% of all suicidal poisonings. In more than 35% of these poisonings, verapamil is the only, or one of the medications (5).

Common clinical manifestations of CCB overdose are nausea and vomiting, hypotension and bradycardia (6). A range of similar adverse effects have been reported in case reports, but death and life threatening complications such as heart block and refractory hypotension are much more common with verapamil than diltiazem (7). Recommended treatments for CCB poisoned patients include gastrointestinal decontamination, bicarbonate, calcium chloride, vasopressors, glucagon and high-dose insulin euglycemic therapy (HIET) (6). Nevertheless, some scientists proposed administration of lipid rescue therapy (LRT) as an alternative treatment for severely CCB poisoned patients (8).

We report a severely poisoned patient with verapamil and furosemide, who was successfully treated with HIET and LRT.

CASE REPORT

A 27-year-old woman (55 kg, 165 cm) was brought to "Mother Theresa" Clinical Center in Skopje with a history of consumption of 24 grams (100 pills) sustained-release verapamil and 4 grams (10 pills) furosemide 4 hours earlier, in a suicidal attempt. She was alert and oriented, while her blood pressure (BP) was 60/35 mmHg, heart rate was 40 beats/min with first degree atrioventricular (AV) block on ECG, and respiratory rate was 25 breaths/min. In the first 90 minutes, she received activated charcoal, 1 liter of 0.9% saline, 60 mL of calcium chloride ($CaCl_2$), 40 mg potassium and subsequently dopamine and 100 mg noradrenaline. However, there was no significant improvement in her hemodynamic status (BP = 70/50 mmHg), and she

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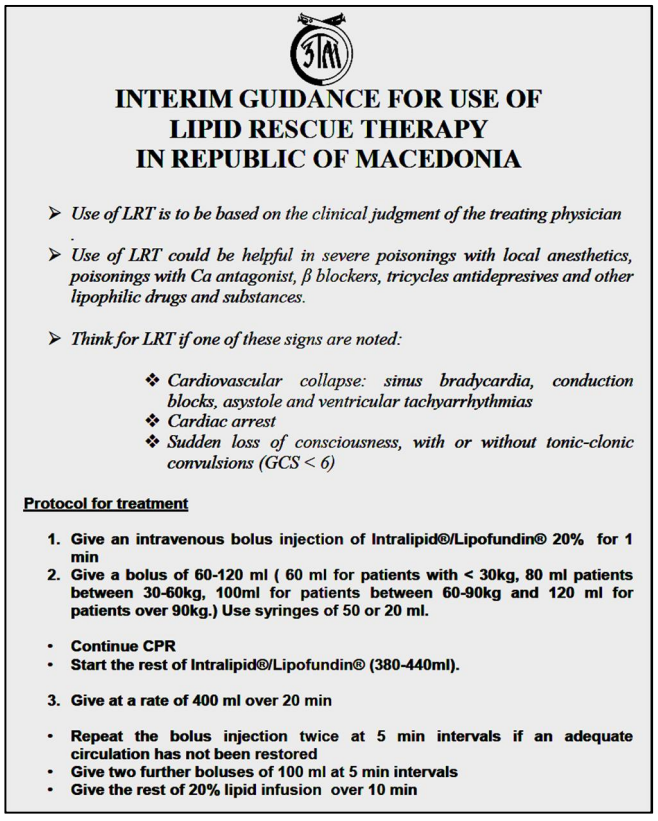
Received 17 July 2013; Accepted 10 September 2013

developed second degree AV block. Temporary pace maker was implanted. In the next one hour, the patient had stable vital signs (BP = 125/65 mmHg), when she again became hypotensive (BP = 60/35 mmHg) with prolonged QRS complex (20 msec). During this period, she was treated with epinephrine (9 mg), atropine (2 mg), isoprenalin, bicarbonate, $CaCl_2$, and intravenous fluid. Unsuccessful conventional treatments indicated administration of HIET and LRT. According to HIET Protocol, 2 ampoules of 50% dextrose and 30 IU intravenous insulin (bolus) was given to the patient and the treatment continued with 500 mL of 5% dextrose with 30 IU intravenous insulin in the next one hour. After 30 minutes, we noticed significant improvement of all hemodynamic parameters (BP = 100/75 mmHg, QRS = 12 msec). Two hours later, she again became hypotensive (BP = 70/40 mmHg) with wide QRS complex. Hence, she was intubated and LRT was initiated according to interim protocol devised for use in Macedonia (Figure 1) (9).



INTERIM GUIDANCE FOR USE OF LIPID RESCUE THERAPY IN REPUBLIC OF MACEDONIA

- *Use of LRT is to be based on the clinical judgment of the treating physician*
- *Use of LRT could be helpful in severe poisonings with local anesthetics, poisonings with Ca antagonist, β blockers, tricycles antidepresives and other lipophilic drugs and substances.*
- *Think for LRT if one of these signs are noted:*
  - *Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias*
  - *Cardiac arrest*
  - *Sudden loss of consciousness, with or without tonic-clonic convulsions (GCS < 6)*

Protocol for treatment

1. **Give an intravenous bolus injection of Intralipid®/Lipofundin® 20% for 1 min**
2. **Give a bolus of 60-120 ml (60 ml for patients with < 30kg, 80 ml patients between 30-60kg, 100ml for patients between 60-90kg and 120 ml for patients over 90kg.) Use syringes of 50 or 20 ml.**

- **Continue CPR**
- **Start the rest of Intralipid®/Lipofundin® (380-440ml).**

3. **Give at a rate of 400 ml over 20 min**

- **Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored**
- **Give two further boluses of 100 ml at 5 min intervals**
- **Give the rest of 20% lipid infusion over 10 min**

Figure 1. Macedonian guidance for the use of lipid resuscitation therapy in acute poisonings. From: Proceedings of IX Symposium of the Macedonian Association of Toxicologists with International participation (with permission)

All hemodynamic and cardiac conduction disturbances disappeared in next 48 hours. BP was 110/75 mmHg 3 hours later and normal ECG was noted 36 hours after LRT. No further disturbances or any recurrence were noted during the next four days, when she left the hospital without any sequels.

DISCUSSION

Conventional treatments for CCB overdose include supportive care, gastrointestinal decontamination, calcium salts, glucagon, HIET and vasopressors including dopamine, dobutamine and norepinephrine (6,9). Most of these treatments are intended to increase trans-membrane calcium flow (calcium salts) or increase of cyclic adenosine monophosphate (cAMP) concentration by stimulating production of adenylate cyclase (with norepinephrine and glucagon), or by inhibiting production of phosphodiesterase (with amrinone and milrinone) (9). However, the conventional treatments may be unsuccessful in reversing the cardiovascular toxicity of CCBs and they commonly fail to improve the hemodynamic condition of the patient (8,9).

Blockade of the L-type calcium channels that mediate the antihypertensive effect of CCBs also decreases the release of insulin from pancreatic β-islet cells and reduces glucose uptake by tissues (insulin resistance) (10). These, in turn, may be the most important factors in CCB-mediated attenuation of cardiac inotropism and peripheral vascular resistance (10). By targeting this insulin-mediated pathway, HIET appears to have a beneficial role, and its clinical potential is under-recognized in the management of severe CCB toxicity (10).

The other alternative treatment which has been recommended and found to be effective is LRT (8,11-14). The predominant theory for its mechanism of action is that by creating an expanded intravascular lipid phase, equilibria are established that can drive the offending drug from target tissues into the newly formed 'lipid sink' (11). Based on this hypothesis, lipid emulsion has been considered as a candidate for reversal of toxicity caused by overdose of any lipophilic drug (11).

There are only a limited number of case reports that presented LRT (± HIET) as a therapeutic measure for CCB overdose. Montiel et al. reported an 18-year-old woman with intentional ingestion of 3600 mg sustained-release diltiazem who developed severe hypotension refractory to routine treatments and finally was treated with HIET and LRT (12). Liang et al. presented a case of 41-year-old woman who ingested 19.2 g of sustained release verapamil in a suicidal attempt (13). For this case HIET did not show any benefit, but she was successfully treated with LRT (13). Willson et al. similarly described a case of refractory cardiogenic shock secondary to sustained release diltiazem poisoning which was effectively treated with LRT, 13 hours post-ingestion; while other treatments were ineffective (14). Yung et al. also reported positive effects of LRT when other treatments failed (8).

CONCLUSION

LRT in addition to HIET are effective treatments for CCB overdose. LRT can be considered as a standard treatment for CCB overdose. Nevertheless, further investigations are necessary to establish the real value of these treatments.

Conflict of interest: None to be declared
Funding and support: None

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