

Treatment of near-fatal beta blocker and calcium channel blocker intoxication with hyperinsulinemic euglycemia, intravenous lipid emulsions and high doses of norepinephrine

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Abstract

Background. Treatment of combined beta blocker and calcium channel blocker intoxication remains challenging due to a profound and treatment-resistant circulatory collapse. Along with standard therapy (calcium, glucagon, mechanical ventilation, vasopressors), two novel approaches are increasingly being reported as successful: hyperinsulinemic euglycemia and intravenous lipid emulsion.

Case Report. Our patient: a 66-year-old Caucasian male who ingested approximately 450 mg of bisoprolol, 300 mg of amlodipine, 200 mg of doxazosin and smaller amounts of nifedipine, torasemide, acetylsalicylic acid and ibuprofen in a suicide attempt. The patient was hypotensive and bradycardic on admission with left-ventricular ejection fraction estimated at 10-15%. By combining standard therapy (intubation, mechanical ventilation, vasopressors, calcium and glucagon) and new therapies (hyperinsulinemic euglycemia and intravenous lipid emulsions) in a stepwise approach we normalized systolic function and treated bradycardia

within 2 hours of admission. However, severe hypotension persisted requiring extremely high doses of norepinephrine (14 mcg/kg/min) and vasopressin (0.03 U/min) to maintain his blood pressure over the following three days. He was discharged home after prolonged in-hospital treatment and rehabilitation (62 days) and extensive physical and psychiatric rehabilitation.

Why should an emergency physician be aware of this? Aggressive medical therapy including hyperinsulinemic euglycemia, intravenous lipid emulsions and high doses of norepinephrine could be considered for multidrug intoxication with a predominant clinical picture of beta blocker and calcium channel blocker intoxication in patients presenting with severe hemodynamic compromise.

Key words: poisoning, emergency treatment, complementary therapies

Introduction

Traditionally, therapy for beta blocker (BB) and calcium channel blocker (CCB) intoxication consisted of calcium and glucagon administration and supportive measures. (1) There are reports of successful use of extracorporeal support in cases of refractory cardiogenic shock. A number of papers have been published describing successful treatment with hyperinsulinemic euglycemia (HIEG) and intravenous lipid emulsions (ILE). (1-5) Animal studies support the use of HIEG and ILE, however optimal timing, duration and dosage of both of these therapies, especially ILE, remains unknown. (4,6-8) We present a case of successful treatment of a near-fatal multidrug intoxication, with BB and CCB intoxication dominating the clinical presentation.

Extremely high doses of norepinephrine and vasopressin were required to maintain our patient's blood pressure. Temporary transvenous pacing or extracorporeal support were not used.

Case report

A 66-year-old male with a history of depression and arterial hypertension was admitted to the intensive care unit (ICU) about 2 hours after taking approximately 450 mg of bisoprolol, 300 mg of amlodipine, 200 mg of doxazosin, 600 mg of nifedipine, 150 mg of torasemide, 4000 mg of acetylsalicylic acid and 5000 mg of

ibuprofen in a suicide attempt. We were able to ascertain quantities of ingested drugs heteroanamnestically. He was unconscious, hypotensive (blood pressure 45/30 mmHg) and bradycardic (sinus bradycardia with heart rate 30 beats per minute (bpm)) on admission. During the peri-intubation period he was supported with 4 boluses (0.1 mg each) of epinephrine. Bedside echocardiography revealed severe left-ventricular systolic dysfunction. Ejection fraction was estimated at 10-15% and velocity-time interval of left ventricle outflow tract (VTILVOT) was 9 cm. Arterial and central venous catheterization was performed next. Initial 10 ml of 10% calcium-gluconate resulted in an increase in heart rate to 40-45 bpm and three more infusions of calcium-gluconate were used during arterial and central venous cannulation. Simultaneously, 5 mg of glucagon was infused, followed by two additional glucagon infusions (5 mg each). A total of 1500 ml of normal saline was infused in the first 30 min without any additional effect on blood pressure. Norepinephrine was started as soon as the central venous catheter was in place. Simultaneously, dobutamine infusion (10 mcg/kg/min) was initiated, without a notable increase in heart rate or ejection fraction. We applied activated charcoal (50 g) after gastric lavage. Qualitative laboratory analysis of returning fluid confirmed the presence of the above mentioned drugs.

After the above therapy, heart rate increased to about 40-50 bpm, however, infusions of calcium and glucagon were needed to maintain it. We used HIEG as next line of therapy. A bolus dose (1 IU/kg) was followed by continuous infusion (1 IU/kg/h). Heart rate stabilized at about 70-80 bpm 1h after admission and no more infusions of calcium or glucagon was required. ILE was used next. 100 ml of 20% lipid emulsion was infused over 5 min and a further 150 ml over 60 min. After 100 ml of ILE, the patient's left-ventricular ejection fraction normalized (estimated at more than 50%, VTILVOT 16 cm, cardiac output estimated at 8 l/min). In spite of this, increasing doses of norepinephrine were required to maintain his mean arterial pressure at 60 mmHg. Vasopressin, at 0.03 U/min, was added, once the norepinephrine infusion rate reached 0.5 mcg/kg/min. In the following hours, a further increase of the norepinephrine dose was required, reaching 14 mcg/kg/min after about 3 hours, after which his blood pressure stabilized.

Our patient's clinical data including therapy, central venous oxygen saturation, urine output, mean arterial pressure (MAP) and heart rate in the first 6 hours are outlined in figure 1. Severe metabolic acidosis (pH 7.12, partial pressure of carbon dioxide (pCO₂) 5.49 kPa, partial pressure of oxygen (pO₂) 10.9 kPa, bicarbonate

(HCO₃) 10.5 kPa, oxygen saturation 92%, lactate 8.5 mmol/l) was present on admission. Creatinine was elevated to 185 µmol/L, C-reactive protein was < 3mg/L and concentration of acetylsalicylic acid on admission was 167 mcg/ml (within normal range). We observed no major abnormalities in other laboratory tests on admission.

24 hours after admission, norepinephrine infusion could be decreased. HIEG therapy was continued until day 3, when the patient was successfully weaned off both HIEG and vasopressin. He required 0.6 mcg/kg/min of norepinephrine on day 3 and 0.1 mcg/kg/min on day 7. Norepinephrine infusion was discontinued on day 17, and the patient was extubated on day 18 and discharged from the ICU on day 25. After having completed psychiatric rehabilitation he was discharged home without neurological sequelae after 62 days.

Discussion

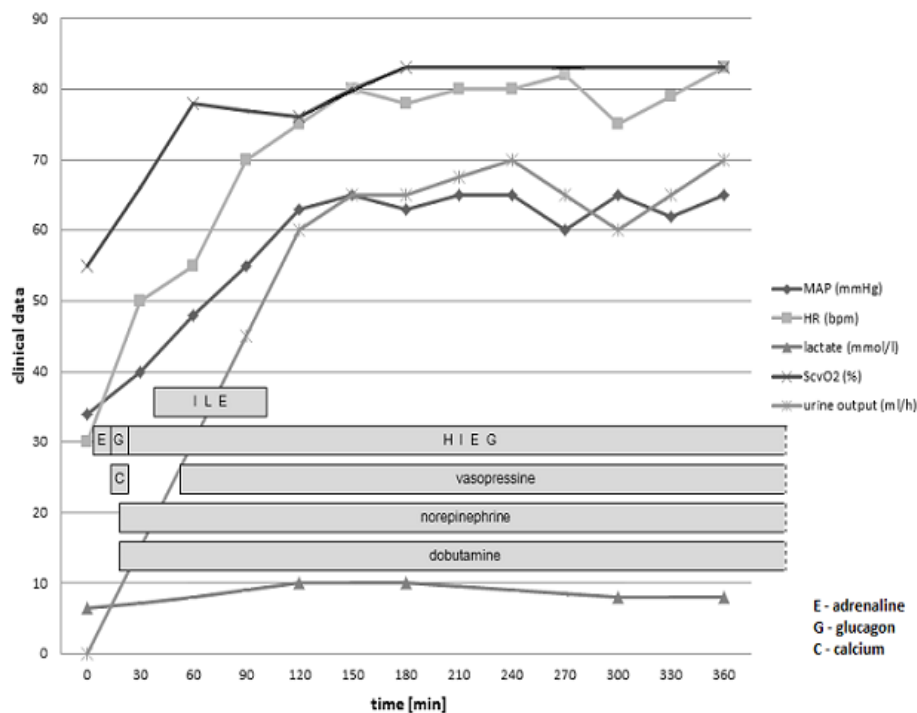
In our patient, severe BB and CCB intoxication caused profound and resistant circulatory collapse. Immediately after admission, we maintained his blood pressure using standard therapy with calcium, glucagon and boluses of epinephrine. This has been described (5) and was partially effective in our case. Because of severe hemodynamic compromise we progressed to HIEG and ILE. HIEG improves cardiac contractility and vascular resistance. (6) Because of inhibition of calcium channels, CCB intoxication causes reduction of glucose uptake and consequent decrease in myocardial contractility and loss of vascular smooth muscle cell function. Animal studies of CCB intoxication have favored HIEG over standard therapy (calcium, glucagon or epinephrine). (6) The optimal dose of insulin in HIEG is not known. Reported doses are 0.5 to 1 IU/kg bolus, followed by 0.5-1 IU/kg/h infusion. Hypoglycemia and hypokalemia are the main adverse effects. (4,6) ILE is a novel treatment for lipophilic drug poisonings, which was first described in local anesthetic poisoning and more recently in cases of other lipophilic drug poisonings, including BB and CCB. (7,8) Animal models of CCB poisoning suggest survival benefit of ILE over standard therapy. (7) Main adverse effects are development of acute lung injury and allergic reactions. (2,7,8) Successful concurrent use of HIEG and ILE has been described in drug-induced cardiogenic shock. (2)

Mechanical support with either intra-aortic balloon pump or veno-arterial extra-

corporeal membrane oxygenation (VA ECMO) was considered from the outset. (9) We decided against it, once systolic function improved after the instituted medical therapy. Use of these devices in vasodilatory shock is questionable. (9) We attributed severe hypotension to ingestion of multiple antihypertensives (5) and treated it with dual vasopressor therapy in high doses. There are reports of successful and safe use of norepinephrine at doses higher than 4 mcg/kg/min. (10) Our patient's fingertips remained warm and well perfused throughout treatment.

In conclusion, aggressive medical therapy for severe multi-drug intoxication with a predominant clinical picture of BB and CCB intoxication including calcium, glucagon, HIEG and ILE, while providing support with norepinephrine and vasopressin is plausible and could be considered early in patients presenting with severe hemodynamic compromise.

Figure 1. Clinical data in the first 6 hours of treatment. HR, heart rate; MAP, mean arterial pressure; ScvO₂, central venous oxygen saturation.



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