ABSTRACT

Aims: Highlighting the efficacy of early initiation of high dose insulin therapy in Beta-blockers overdose over conventional therapy.

Presentation of Case: Authors describe the successful treatment of severe bisoprolol-induced cardiogenic shock in a 74-year-old man using high dose insulin euglycemic therapy. He received intravenous bolus of 1IU/kg of actarapid insulin followed by intravenous infusion of 0.5 IU/kg/hour. The patient hemodynamic parameters improved dramatically within few hours after starting the insulin therapy.

Discussion: Beta-blockers overdose can lead to significant morbidity and mortality due to the often-associated vasopressor-resistant shock. High dose insulin euglycemic therapy is a potential emerging therapy for beta-blockers toxicity with support in the literature from several animal studies, case reports and expert opinion.

Conclusion: High dose insulin euglycemic therapy is a safe and effective method in reversing the hemodynamic consequences induced by beta-blockers overdose and should be used early in the treatment.
Keywords: Beta-blockers; cardiogenic shock; inotropes; insulin; case report.

1. INTRODUCTION

Beta-adrenergic receptor antagonists (beta-blockers) have been used in clinical practice for more than 50 years and are among the most prescribed medications. Although safe when taken in normal therapeutic doses, beta-blockers overdose can cause significant morbidity and mortality. In severe cases, it can lead to significant reduction in the cardiac output and cardiogenic shock which are clinically challenging to manage. The conventional management of beta-blockers poisoning includes intravenous fluids, atropine, glucagon, vasopressor, inotropic support, and cardiac pacing [1]. However, the response to the conventional therapy is usually limited in patients with severe toxicity. Insulin has a great role in the control of intermediary metabolism and besides its metabolic functions; it has important actions on steroidogenesis, vascular function, fibrinolysis and normal growth. Moreover, studies showed that high dose insulin infusion in normal, healthy volunteers resulted in an increase in stroke volume and ejection fraction [2]. The use of high dose insulin euglycemic therapy (HDIET) in beta-blockers overdoses is supported by experimental evidence in animals' studies and case reports [3-5]. It was usually reserved as a last rescue therapy, however, it is being frequently used early in treating calcium channel blockers overdose, beta-blockers overdose, as well as mixed overdose [6]. In our case report, we demonstrated the quick improvement of beta-blockers induced cardiogenic shock after starting the HDIET.

2. PRESENTATION OF CASE

A 74-year-old, 90-Kg male with a past medical history of hypertension, non-insulin dependent diabetes mellitus and ischaemic heart disease was brought by ambulance after being found unresponsive following taking unknown amounts of bisoprolol, metformin and sitagliptin while intoxicated. He was given 1.2 mg of atropine and 1 l of compound sodium lactate intravenously by paramedics for sinus bradycardia with a pulse of 28 beats per minute (bpm). On examination in emergency department, he was drowsy and confused, his Glasgow Coma Scale was 13/15, there were bilaterally equal and reactive pupils, blood pressure (BP) 65/32 mmHg, pulse 32 bpm, cold extremities with capillary refill time of 5 seconds, respiratory rate of 32 breaths per minute with Kussmaul pattern of breathing and SpO2 of 99% on 10 l.minute⁻¹ oxygen mask.

On examination, he had equal air entry on both lungs, normal heart sounds and his abdomen was soft and non tender. His electrocardiogram showed sinus bradycardia and arterial blood gas showed lactic acidosis with lactate 13.3 mmol.L⁻¹, PaO₂ 11.3 KPa, PaCO₂ 2.8 KPa, bicarbonate 10.1 mmol.L⁻¹ and base excess of -14.3 mmol.L⁻¹. Other blood investigations showed haemoglobin 113 g.l⁻¹, white cell count 12.9 × 10⁹.l⁻¹, platelets 396 × 10⁹.l⁻¹, Sodium 135 mmol.L⁻¹, Potassium 4.8, mmol.L⁻¹, urea 4.3 mmol.L⁻¹, creatinine 142 mmol.L⁻¹, glomerular filtration rate of 26 ml.minute⁻¹ (Cockcroft-Gault method), and normal coagulation. His chest X-Ray showed right perihilar infiltrate.

He was given additional 1.8 mg of atropine, 60 mg of ephedrine, 2 mg of glucagon and 2 l of intravenous fluids but with no response. Adrenaline infusion was started in a peripheral intravenous 16 G cannula and adrenaline boluses of 300 micrograms (total of 1.8 mg over 15 minutes) were given till central venous access was obtained then central venous adrenaline (15 microgram/minute) and noradrenaline infusion (20 microgram/minute) were commenced to keep mean arterial BP between 50 - 60 mmHg.

After admission to the intensive care unit (ICU), the UK toxicology service was contacted and recommended starting high dose insulin euglycemic therapy (HDEIT) to manage the beta blockers toxicity and renal replacement therapy to manage the metformin toxicity if Lactate remains high. One IU.kg⁻¹ of actarapid insulin was given intravenously followed by intravenous infusion of insulin 0.5 IU.kg⁻¹.hour⁻¹ and Glucose 10% solution at 100 ml.hour⁻¹. Serum electrolytes and glucose were monitored every hour and 50 ml of Glucose 50% was given if blood glucose was less than 10 mmol.L⁻¹. Over the next few hours, adrenaline and noradrenaline requirements decreased dramatically and were discontinued after 7 hours of starting HDEIT [Table1]. The Insulin infusion was weaned slowly afterwards then glucose infusion was weaned 6 hours later. Lactate levels normalised within 48 hours. The patient's ICU
course was complicated by pulmonary edema which was managed by diuretics and non-invasive continuous positive airway pressure (CPAP). He was maintaining his airway and spontaneous breathing throughout admission and discharged to ward after 4 days.

3. DISCUSSION

Beta-blockers have a broad range of application in clinical practice especially in the treatment of cardiovascular diseases. They exert their actions through competitive blocking of beta-adrenergic receptors. There are three subtypes of beta-adrenergic receptors; beta-1 receptors are predominantly present in the myocardial tissue, beta-2 receptors are mainly in the bronchial smooth muscles, and beta-3 receptors are present in adipose tissue as well as the heart. Beta-blockers are traditionally classified as either selective (blocking beta-1 receptors) or non-selective, however, the selectivity is usually maintained in therapeutic rather than toxic levels.

Bisoprolol is a selective beta-1 adrenoceptors antagonist. It is rapidly absorbed after oral administration with bioavailability of 80%, has moderate lipid solubility, and has a half-life of 9-12 hours which can be prolonged up to 36 hours if creatinine clearance is less than 40 ml/minute [1].

In the heart, blocking of beta-1 adrenoceptors leads to reduction of calcium influx in cardiac myocytes due to reduction in adenylate cyclase activity decreasing the synthesis of cyclic adenosine monophosphate (cAMP) which control L-type calcium channel opening. Excessive beta-adrenergic antagonism seen in beta-blockers toxicity leads to significant myocardial depression and cardiogenic shock due to depressed contractility in myocytes, reduced spontaneous depolarization in pacemaker cells as well as blocking of impulses transmission through the conduction pathway [6].

The main goals of the specific management of beta-blockers overdose are to restore the cardiac output and organ perfusion. Several therapeutic agents are usually used simultaneously including glucagon, calcium, atropine and sympathomimetics, however, the clinical response to those agents can be inadequate to improve the patient condition and restore tissue perfusion.

Glucagon is usually considered a first-line agent, despite the lack of human studies and absence of survival benefits from animal studies [1]. Similarly, animal studies and case reports showed that the sole use of catecholamine in the treatment of beta-blockers toxicity resulted in poorer outcomes probably because of the detrimental effect of increasing the systemic vascular resistance and myocardial oxygen consumptions which might further decrease the cardiac output [7,8].

To the authors’ knowledge, there is no published case report about the use of high dose insulin in bisoprolol overdose. In this report, we demonstrated successful treatment of severe cardiogenic shock induced by bisoprolol overdose, which was refractory to traditional measures, using HDIET. The patient’s hemodynamic measurements improved quickly after initiation of the insulin therapy and the inotropic support was weaned within 7 hours.

HDIET is emerging as a potential antidote for calcium channels blockers and beta-blockers toxicity, and it might replace the traditional first-line agents. [8]. Insulin can effectively reverse cardiac depressant effects of these agents through different mechanisms including increased myocardial contractility, improved

| Time | 0:00 | 1:00 | 2:00 | 3:00 | 4:00 | 5:00 | 6:00 | 7:00 | 8:00 |
|------|------|------|------|------|------|------|------|------|------|
| Noradrenaline (microgram/minute) | 20 | 20 | 20 | 30 | 30 | 20 | 16 | 12 | off |
| Adrenaline (microgram/minute) | 15 | 14 | 14 | 14 | 14 | 10 | 8 | 4 | off |
| Insulin (unit/hour) | 0 | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 |
| Blood pressure (mmHg) | 92/44 | 97/46 | 99/47 | 89/42 | 101/47 | 107/50 | 132/71 | 120/59 | 121/55 |
| pH | 7.29 | 7.33 | 7.25 | 7.29 | 7.35 | 7.39 | 7.4 | 7.4 | 7.4 |
| pCO₂ (Kpa) | 2.8 | 2.3 | 2.6 | 3.3 | 3.4 | 3.2 | 3.6 | 3.6 | 3.6 |
| Lactate (mmol.l⁻¹) | 13.3 | 13.7 | 12.8 | 10.8 | 8.6 | 6.6 | 5.1 | 5.1 | 5.1 |
| Bicarbonate (mmol.l⁻¹) | 10.1 | 9 | 8.3 | 12 | 14.4 | 14.5 | 16.7 | 16.7 | 16.7 |
| Base excess (mmol.l⁻¹) | -14.3 | -14.3 | -16.7 | -12.8 | -9.5 | -8.6 | -6.6 | -6.6 | -6.6 |
intracellular glucose metabolism, and enhanced microvascular circulation [8]. Contrary to catecholamine, insulin enhances the cardiac function with neither increasing the heart rate nor myocardial oxygen demand [7].

Several studies showed improvements of left ventricular function in patients with myocardial infarctions following high dose insulin and glucose infusions, which were similar to a low dose dobutamine infusion [2,9]. Furthermore, Insulin increases myocardial glucose uptake thus improving the fuel sources for the myocardium, which switch from its normal free fatty acids to glucose for energy utilizations during stress conditions. Also, Insulin has been found to increase nitric oxide production in the microcirculation by stimulating nitric oxide synthetase in the vascular endothelium. The resultant vasodilatation improves the flow in the peripheral circulation thus improving cardiac output [2,8].

In a swine model, Holger et al compared high dose insulin versus adrenaline and vasopressin in propranolol overdose [7]. They terminated their study early after five pigs were recruited in each arm due to significant survival differences as all pigs received adrenaline and vasopressin died within 90 minutes compared to 100% survival in the insulin group. Kerns et al demonstrated the superiority of high dose insulin over glucagon and adrenaline infusions in the treatment of acute beta-blockers toxicity in dogs [5]. Insulin was shown to improve left ventricular function and blood pressure without altering the heart rate.

Cole et al conducted a retrospective chart review study about high dose insulin in beta-blockers’ and calcium channels blockers’ overdoses [8]. They demonstrated the safety and efficacy of using high dose insulin in this setting and recommended its early initiation by emergency physicians.

There is no consensus regarding the dosing of HDIET in beta-blockers overdose. In Cole et al study which compared three doses of HDIET in propranolol-induced cardiogenic shock, cardiac output was found to directly increase with increasing the insulin dose [10].

Krenz et al recommended in their review an intravenous dose of 1 IU.Kg	extsuperscript{-1} of insulin followed by continuous infusion of 0.5 – 1 IU.Kg	extsuperscript{-1}.hour	extsuperscript{-1}, titrated upward every 15 minutes if no clinical response up to 10 IU.Kg	extsuperscript{-1}.hour	extsuperscript{-1} [6].

Although HDIET is well tolerated by patients with no major adverse effects, it can be associated with metabolic disturbances (hypokalemia from intracellular shift and hypoglycemia) and fluid overload due to the concomitant use of glucose infusion [4,8]. Regular monitoring of serum electrolytes and glucose with adequate replacement can prevent these potential disturbances. Also, Fluid balance should be vigilantly monitored during HDIET to avoid fluid overload especially in patients with borderline renal functions.

4. CONCLUSION

HDIET is a safe and effective method in treating severe beta-blockers toxicity, which should be used early as a first line agent. Although it can be initiated in the emergency department, it is better to be given in a critical care setting due to the potential metabolic disturbances associated with its use, provided that treatment will not be delayed. Further human trials are needed to establish the exact mechanism of action and the most effective dosing regimen.

CONSENT
Published with the written consent of the patient.

ETHICAL APPROVAL
As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES

1. Fermin Barrueto. Beta blocker poisoning. Up To Date; 2018. Available:www.uptodate.com/contents/beta-blocker-poisoning Accessed 01/12/2019.
2. Klein LJ, Visser FC. The effect of insulin on the heart: Part 1: Effects on metabolism and function. Neth Heart J. 2010 4:197-201.
3. Page C, Hacket LP, Isbister GK. The use of high-dose insulin-glucose euglycemia in beta-blocker overdose: A case report. J Med Toxicol. 2009;5:139–143.
4. Lyden AE, Cooper C, Park E. Beta-blocker overdose treated with extended duration high dose insulin therapy. J Pharmacol Clin Toxicol. 2014;2:1015.

5. Kerns W, Schroeder D, Williams C, Tomaszewski C, Raymond W. Insulin improves survival in a canine model of acute beta-blocker toxicity. Ann. Emerg. Med. 1997;29:748-757.

6. Krenz JR, Kaakeh Y. An overview of hyperinsulinemic-euglycemic therapy in calcium channel blocker and β-blocker overdose. Pharmacotherapy. 2018;38:1130-1142.

7. Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, Flottemesch TJ. Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. Clin. Toxicol. 2007;45:396-401.

8. Cole JB, Arens AM, Laes JR, Klein LR, Bangh SA, Olives TD. High dose insulin for beta-blocker and calcium channel-blocker poisoning. Am J. Emerg Med. 2018;36:1817-1824.

9. Devos J, Peeters A, Wittebole X, Hantson P. High-dose insulin therapy for neurogenic-stunned myocardium after stroke. BMJ Case Reports. 2012;2012:bcr2012006620.

10. Cole JB, Stellpflug SJ, Ellsworth H, et al. A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock. Clin. Toxicol. 2013;51:201-207.

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