The Use of High-Dose Insulin-Glucose Euglycemia in Beta-Blocker Overdose: A Case Report

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ABSTRACT

The management of life-threatening beta-blocker toxicity and its associated low cardiac output state is clinically challenging. Previous case reports and case series describe the use of hyperinsulinemia/euglycemia therapy in mono-ingestions of calcium channel blockers and mixed ingestions, including calcium channel and beta-blockers. In this case report we describe the use of high-dose insulin (10 IU/kg per hour) in a case of massive metoprolol ingestion (5 g) in which hypotension was unresponsive to conventional therapies. Although the metoprolol concentrations measured in plasma were approximately 100–200 times therapeutic concentrations, the pharmacokinetics appeared to be similar to therapeutic metoprolol dosing.

INTRODUCTION

Metoprolol is a beta-1 selective adrenoceptor-blocking drug that is used therapeutically in the treatment of hypertension, angina, myocardial infarction, migraines, arrhythmias, and as an adjunct in the management of thyrotoxicosis [1]. Its toxicity in overdose results from direct myocardial depression and impaired myocardial conduction, leading to bradycardia, hypotension, and in large ingestions, life-threatening cardiogenic shock [2]. Central nervous system (CNS) toxicity, including seizures and coma, are uncommon in metoprolol overdose in comparison to more lipophilic beta-blockers (BBs) like propranolol [3].

The specific management of beta-blocker overdose includes the use of atropine, glucagon, isoprenaline, epinephrine, and other inotropes, such as phosphodiesterase inhibitors. These treatments sometimes have limited effectiveness in severe cases of beta-blocker overdose [4,5]. High-dose insulin with glucose supplementation, known as hyperinsulinemia/euglycemia therapy (HIE), has been advocated for the management of BB toxicity based on its use in calcium channel blocker (CCB) poisoning and increasing evidence in animal studies [4,5]. Successful treatment for beta-blocker toxicity using HIE was first studied in dogs [6]. Further animal studies [7,8] using a propranolol model also supported its benefit. To date there are no published human case reports of using HIE in beta-blocker toxicity, although there are reports in CCB and combined CCB and BB ingestions [5]. Doses of insulin have ranged from 0.1 to 2.5 IU/kg per hour, with 0.5–1.0 IU/kg per hour being the most commonly used regimen [5]. Recently, HIE using insulin at doses of up to 10 IU/kg per hour was shown to be more effective than combined epinephrine and vasopressin in a swine model of BB toxicity [9].

Keywords: high-dose insulin, euglycemia, beta-blocker toxicity
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Here we report the use of HIE in a metoprolol ingestion using higher doses of insulin than previously described in human case reports of CCB and mixed CCB/BB ingestions when hypotension was unresponsive to conventional therapy.

CASE REPORT

A 45-year-old, 50-kg woman presented to the emergency department (ED) approximately 2 hours after ingesting 5 g (one hundred 50-mg tablets) of metoprolol and an unknown quantity of alcohol. The patient and family confirmed the dose on arrival to the ED. On arrival the patient was noted to be confused, with a Glasgow Coma Scale (GCS) of 14 (eyes [E], 4; verbal [V], 4; motor [M], 6), a heart rate (HR) of 54 beats per minute (bpm) and a blood pressure (BP) of 86/61 mmHg (112/82 mmHg prehospital). Her temperature was 34.4°C, blood glucose of 5.1 mmol/l [(92 mg/dl) (normal 3.5–7.0 mmol/l or 63–126 mg/dl)] and a capillary return of <2 seconds. The rest of her physical examination was normal. An electrocardiogram (ECG) taken soon after arrival revealed a sinus bradycardia of 54 bpm, and a PR interval of 222 msec with normal QRS and QT intervals. Her only past history included episodes of supraventricular tachycardia for which she was on metoprolol 25 mg twice daily, although she was noncompliant.

Within 1 hour of arrival to the ED and approximately 3 hours after ingestion, her BP suddenly fell to 52/30 mmHg with an unchanged heart rate of 54 bpm (Figure 1A). She became less responsive with a GCS of 11 (E2, V4, M5) and her peripheral circulation and capillary return was poor. The metoprolol concentration at this time was 13.57 mg/L (therapeutic range 0.035–0.125 mg/L; *Figure 2*) [10]. Initial management included atropine 3-mg IV (intravenous) over 15 minutes and fluid loading with 3 L of normal saline (0.9%) over 60 minutes. Despite some clinical improvement she remained hypotensive, with a BP of 68/48 mmHg and HR of 75 bpm.

Four insulin boluses of 1–2 IU/kg based on a weight of 60 kg (60 IU) were administered for a total of 300 IU over 55 minutes with boluses of 50% glucose (50–75 ml/hour) to maintain euglycemia. Blood sugars were measured every 15–30 minutes while in the ED. Over the next hour, her BP climbed to 82/59 mmHg before falling to 72/40 mmHg with a HR of 78 bpm. Two isoprenaline boluses of 40 μg and 80 μg followed by an infusion of 2 mg/hour (33 μg/min) increased her BP marginally to 80/43 mmHg with a HR of 92 bpm.

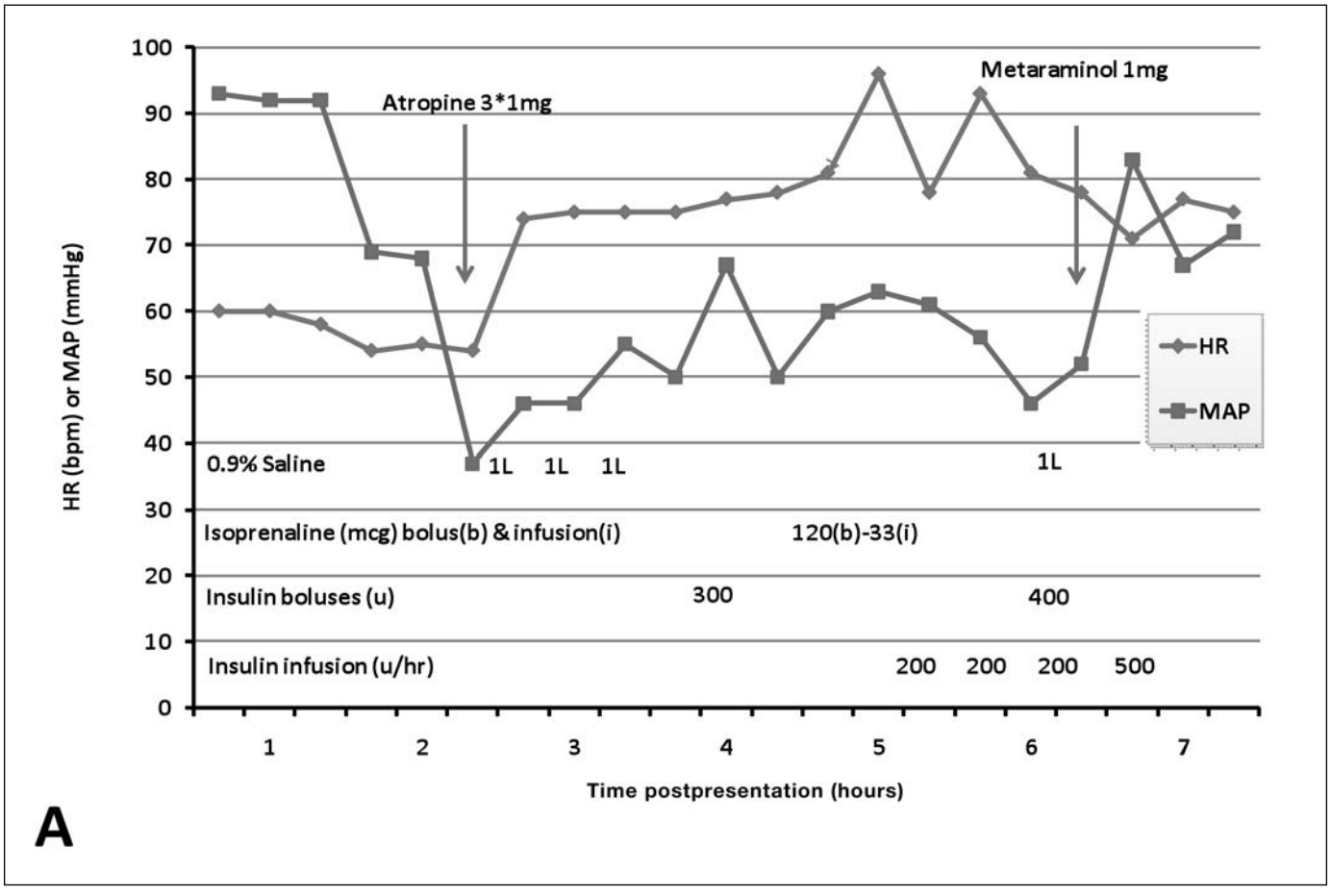


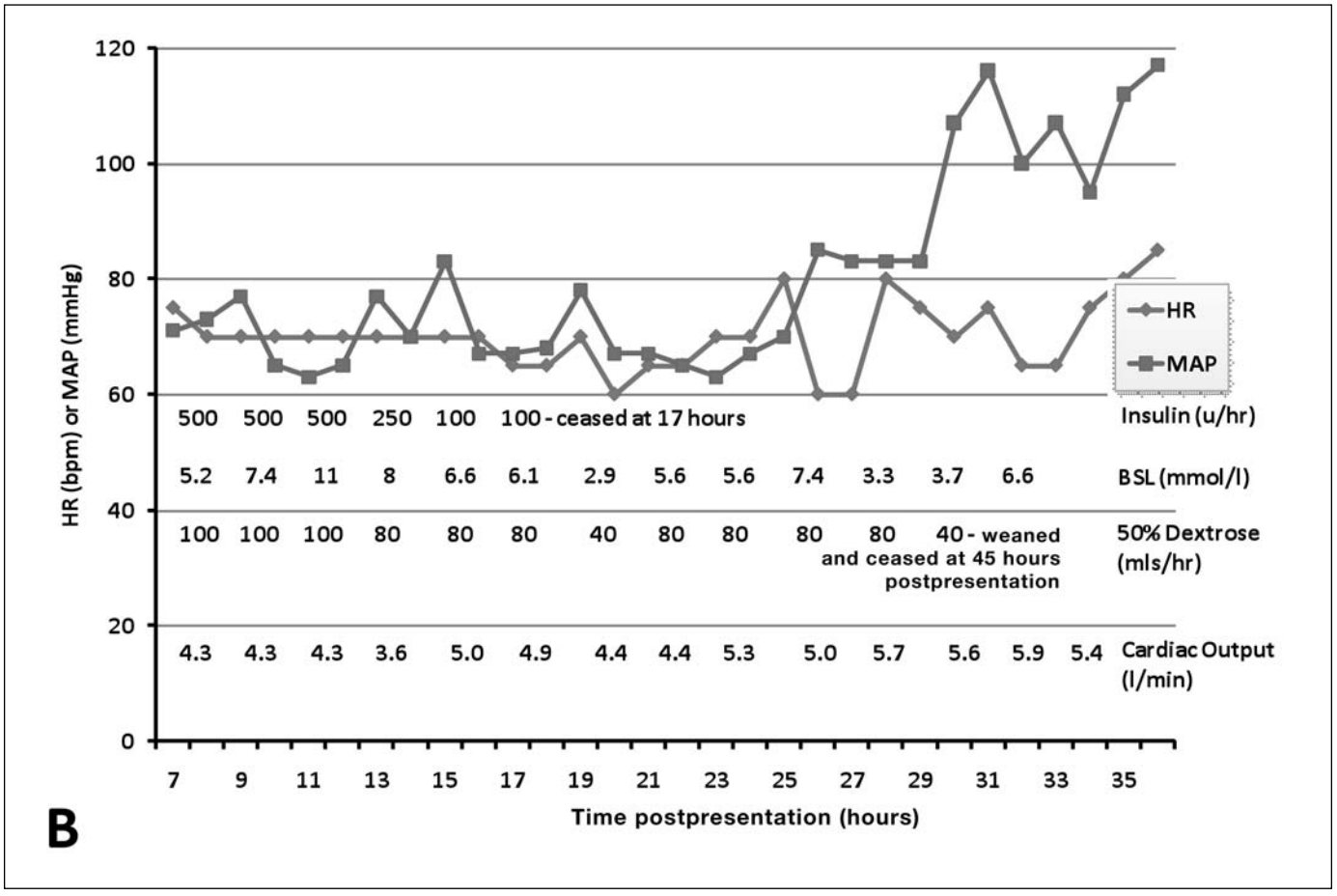
Figure 1: Haemodynamic measurements and important interventions for the first 7 hours in the Emergency Department (A) and the subsequent 29 hours (8-36 hours post presentation) in the Intensive Care Unit (B). (HR = heart rate, MAP = mean arterial pressure, BSL = blood sugar level)

Her extremities were still cold with poor capillary return, and she remained confused. Isoprenaline was discontinued and an insulin infusion was started at 200 IU/hour. Her BP initially fell and then rose after a further 2 boluses of 200 IU of insulin over 5 minutes and 1 L of normal saline to 90/62 mmHg, showing an improvement in clinical condition with a good pulse volume and peripheral circulation as well as improvement in mental status. A sharp rise and fall in her BP from a single 1-mg dose of metaraminol (short-acting alpha agonist) was briefly seen during this period. The metoprolol concentration approximately 7 hours postingestion was 7.75 mg/L. The patient was then transferred to the intensive care unit (ICU).

In the ICU the patient's condition remained stable, with no episodes of hypotension on an insulin infusion of 500 IU/hour (10 IU/kg per hour, based on a revised weight of 50 kg) *(Figure 1B)*. The HR varied between 60 and 80 bpm, MAP between 60 and 85 mmHg, and a urine output >1 mL/kg per hour. No other cardioactive medications were required. The insulin was weaned over 14 hours and finally ceased 17 hours postingestion. The metoprolol concentration at this time was 0.75 mg/L. While in the ICU, cardiac outputs were recorded continuously via a noninvasive cardiac output monitor (Vigileo, Edwards Life Sciences, Irvine, CA) with cardiac outputs of between 3.6 and 5 L/min (70–100 mL/kg). Euglycemia was maintained with 50% dextrose at rates of 0.5–1.0 g/kg per hour (1–2 mL/kg per hour), and there were no episodes (measured hourly) of hypoglycemia (<3.5 mmol/L). Potassium was maintained (maximum rate of 20 mmol/hour) at a low normal concentration (3.5 mmol/L) as the resultant hypokalemia was likely due to cellular shifts and not total body depletion. The patient was discharged well with no sequelae from the ICU 60 hours postingestion with a BP of 120/70 mmHg and a pulse rate of 70 bpm that first occurred 26 hours postpresentation.

DISCUSSION

Beta-blockers, by competitively antagonizing beta-receptors, exert their toxicity primarily through their negative inotropic effect on the myocardium, and treatment is therefore primarily aimed at restoring cardiac output (CO) [10]. Catecholamines are a logical choice and all agents commonly available (e.g., dopamine, dobutamine, epinephrine) have been utilized in BB poisoning with variable success [5]. Isoprenaline, a nonselective beta-agonist, is the obvious choice on theoretical grounds in pure BB poisoning, but case series have not supported this [11]. Even large doses of combinations of catecholamines still often fail to successfully restore CO [11]. Unlike CCB toxicity that decreases both systemic vascular resistance (SVR) and CO, for which an agent with combined alpha-and beta-agonist properties such as epinephrine



would be expected to be beneficial, alpha-agonist activity is likely to be less helpful in pure BB toxicity.

In a swine model of BB toxicity [9] using propranolol and invasive hemodynamic monitoring, insulin was compared to a combination of vasopressin and epinephrine. In the vasopressin and epinephrine group, increasing doses of both agents caused a fall in CO that was compensated by increases in SVR to maintain BP. Ultimately as toxicity worsened, the BP and SVR fell as the CO continued to fall, and death ensued. This is a possible explanation as to why these inotropic agents can be unsuccessful in severe beta-blocker toxicity. They appear to initially maintain BP by increasing SVR, which, in a failing heart, ultimately can be detrimental. Conversely, the addition of insulin at doses of up to 10 IU/kg per hour increased the CO back to baseline and beyond with a trend to a slight fall in BP and SVR, with survival in all the animals. This provides some evidence that the insulin reversed the primary toxicity of the propranolol [9]. The hemodynamic data in our case is consistent with this finding, with a normal to high CO and a low-normal BP being achieved with insulin alone.

Multiple blood samples were collected and metoprolol concentrations were measured, displayed in Figure 2. Metoprolol pharmacokinetics have been studied in therapeutic use with one study reporting peak plasma concentrations that averaged 0.072 mg/L (range 0.035–0.125 mg/L) at 0.8 to 2.5 hours with a mean half-life of 3.8 hours after a single 50-mg oral dose [12]. The approximate peak concentration of 13.57 mg/L in this case report is about 200 times the mean peak concentration seen with a 50-mg dose. When the patient was stabilized on insulin only, the concentration was approximately 100 times this mean concentration. There was no evidence of dose-dependent kinetics in overdose, and the half-life estimate of 2.8 hours was consistent with the short half-life in therapeutic pharmacokinetic studies [1,12].

In this case report and others of this nature, drawing conclusions about any individual intervention in a case that involves the simultaneous use of multiple interventions is difficult. In addition, metabolism of metoprolol may have also contributed to the apparent clinical improvement, particularly since metoporol has a short half-life.

This case describes the use of very high-dose insulin in massive BB overdose. There were no major adverse effects and an apparent improvement in hemodynamics associated with the time of the treatment. It is likely that multiple interventions will be required in BB poisoning, although the focus must be on treating the primary negative inotropic effect. Invasive BP and CO monitoring is essential to better understand both the toxic effect of BBs and the physiological effects of agents used to counteract their toxicity.

The authors have no potential financial conflicts of interest to report.

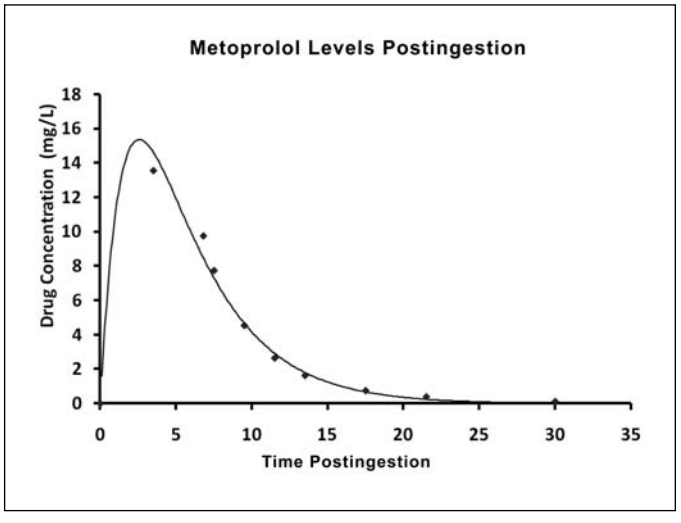


Figure 2: The metoprolol concentration time data was modeled using NONMEM vs 6 (GloboMax, Hanover, MD). The final model was a 1-compartment model with first-order absorption and a combined additive and proportional residual error model was used. The difference in the objective function values was used for hypothesis testing. The final parameter estimates were Clearance (CL/F) 42L/hr, Volume of distribution (Vd/F) 174L and Absorption rate constant (Ka) 0.582L/hr. The derived parameter elimination half-life was 2.8 hours.

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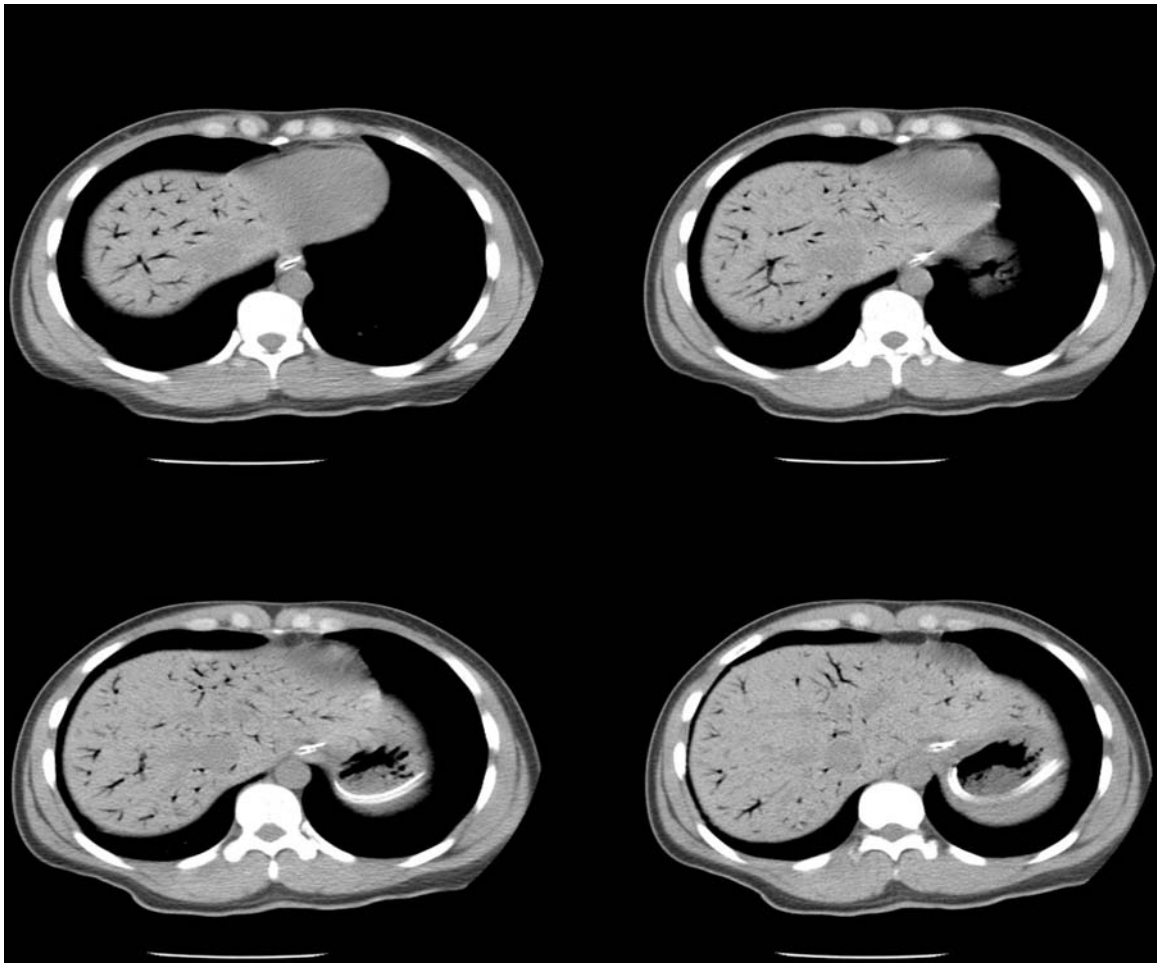
BRIEF TOXICOLOGY COMMUNICATIONS

What Is the Perinent Finding and an Explanation for the Cause?



For the answer, see page 149