

## Introduction

Beta blocker toxicity is an easily missed diagnosis because it presents with non-specific symptoms such as bradycardia, hypotension, and altered mental status. Unless the history of beta blocker overdose is discovered, the symptoms of beta blocker toxicity can remain refractory to supportive treatment. This case report illustrates acute beta blocker toxicity that masqueraded as sepsis and resulted in hemodynamic instability until the underlying etiology became known.

### What is the epidemiology of beta blocker overdose?

Beta blockers serve as first-line treatment for coronary artery disease, the most common cause of death and inpatient hospitalization in the United States. With 65 million prescriptions filled in 2017 and a narrow therapeutic index, beta blockers have the second-highest rate of inadvertently doubled dose of home medication and the second-most reported cases of adverse side effects in the outpatient setting. Beta blockers are also seen in 22% of overdose cases involving cardiovascular drugs in the emergency department (ED). Clinically, metoprolol is the beta blocker most often involved in fatal and non-fatal cases of overdose but propranolol has the highest odds of exposure. Despite initial concerns, extended-release versions of propranolol and metoprolol are associated with low rates of toxicity.

Agent	Prescriptions Filled in 2017 <sup>a</sup>	Deaths in 2017 <sup>b</sup>	Odds of Exposure
Metoprolol (XR)	20,970,347	7	0.21
Metoprolol	20,190,175	58	1.78
Carvedilol	14,338,224	19	0.82
Atenolol	9,908,201	10	0.62
<b>Propranolol</b>	<b>1,667,736</b>	<b>17</b>	<b>6.31</b>
Nebivolol	1,485,994	2	0.83
Labetalol	879,531	1	0.70
Propranolol (XR)	612,943	0	0.00
Bisoprolol	535,835	0	0.00

**Table 1.** Approximately 65 million prescriptions for beta blockers were filled in 2017 in the United States. In the same year, 118 deaths with beta blockers metabolites were verified by autopsy. Metoprolol tartrate contributed 28.6% of filled prescriptions and was associated with 49.1% of overdose deaths. In comparison, propranolol contributed 2.4% of filled prescriptions and was associated with 14.4% of overdose deaths. Standardized odds of exposure are shown where 1.00 is the expected value if listed agents had equal likelihoods of fatality. Extended-release formulations of metoprolol and propranolol were not more likely to be associated with overdose deaths.

<sup>a</sup>Centers for Medicare and Medicaid Services, 2017  
<sup>b</sup>American Association of Poison Control Centers' National Poison Data System, 2017

### What is the pathophysiology of beta blocker toxicity?

The main pharmacological effect of beta blockers is antagonism of  $\beta_1$  and  $\beta_2$  receptors found primarily in heart muscle and peripheral vascular smooth muscle, respectively. All beta blockers decrease heart rate by antagonizing  $\beta_1$  receptors but some cardio-selective agents also directly decrease blood pressure by antagonizing  $\beta_2$  receptors.

In addition to the effects described above, certain beta blockers possess membrane-stabilizing effects that inhibit myocardial action potentials at supratherapeutic levels. This can result in a widened QRS interval on EKG and subsequently lead to ventricular arrhythmia. Other beta blockers are lipophilic and can easily cross the blood-brain barrier, causing effects on the central nervous system (CNS) such as seizures. Propranolol possesses strong membrane-stabilizing effects and lipophilicity and is also the beta blocker most likely to be seen in cases of overdose.

## Case Description

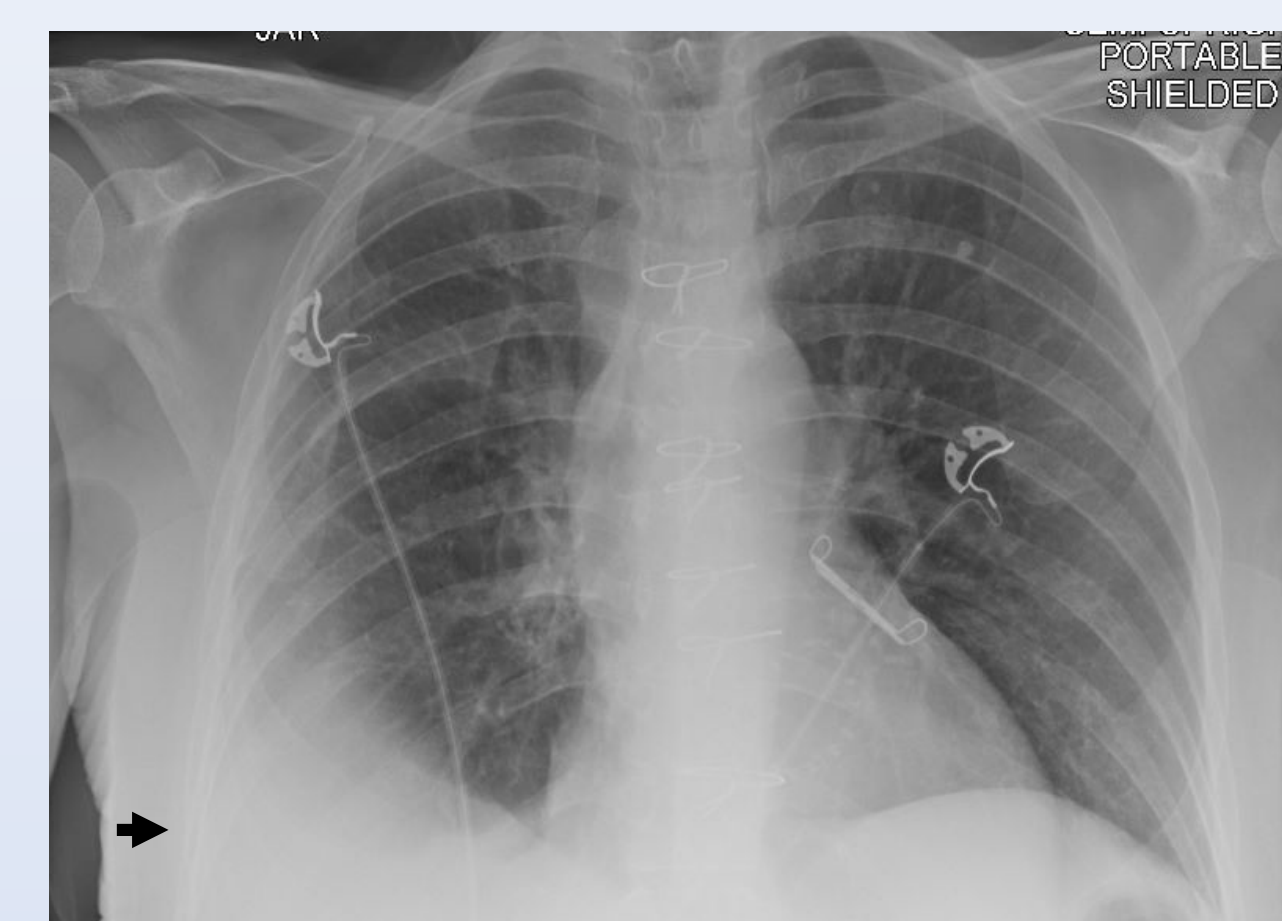
A 58-year-old Caucasian woman with a history of depression, hypertension, and hypothyroidism was brought in by ambulance to the ED for altered mental status. Her vital signs were unstable on arrival with temperature of 36.8°C, heart rate (HR) of 57 bpm, blood pressure (BP) of 68/40mm Hg, and respiration rate (RR) of 20 breaths/min. Her Glasgow Coma Scale (GCS) was 13. Initial labs were remarkable for leukocytosis of 14.5 and lactic acidosis of 3.03. She was presumed to be septic and sepsis protocol was initiated with 30mL/kg IV fluid administration and broad-spectrum antibiotics given. A source of infection was searched for which demonstrated a negative urinalysis and chest x-ray with right-sided pleural effusion without evidence of focal consolidation. Urine and blood cultures would later prove to be negative and the effusion would later prove to be transudative and incidental to her presentation. However, she was presumed to have sepsis secondary to pneumonia at the time.

EKG showed sinus bradycardia and mild QTc prolongation to 451ms. Toxic ingestion of substances was considered as part of the differential diagnosis given her altered mental status and unstable vital signs but her urine drug screen was negative for all tested substances, including acetaminophen and salicylates, although her blood alcohol content was measured at 0.235. Hypothyroidism was not considered as it was not documented in past chart review at the time of presentation. Despite receiving 3 liters of IV fluids, she remained hemodynamically unstable with HR of 57bpm, BP of 86/47mm Hg, and GCS 13. Co-ingestion of a prescribed medication was suspected given her acute alcohol intoxication and upon re-examination, the patient admitted to ingesting approximately 2 grams of metoprolol in an act of self-harm. 3mg of glucagon were promptly ordered per treatment guidelines. However, she responded after receiving just 1mg of glucagon with vital signs to HR of 75 bpm, BP of 114/75mm Hg, and GCS of 15 within minutes. The remaining 2mg of glucagon were withheld in favor of placing her on an IV glucagon drip at a rate of 2mg/hr. She received 10 hours of glucagon infusion after which her vital signs remained stable. She was discharged to home after evaluation by a psychiatrist.

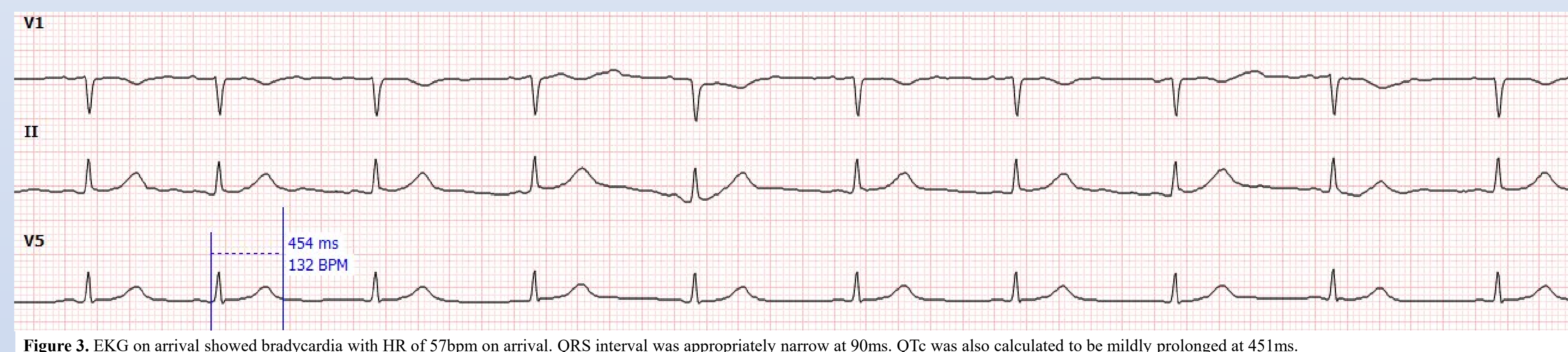
Labs and Vitals					
T	36.8°C	→	36.8°C	→	36.8°C
HR	57bpm*	→	57bpm*	→	75bpm
BP	68/30mm Hg	→	86/47mm Hg	→	114/75mm Hg
RR	20/min		20/min		20/min
GCS	13*		13*		15
WBC	14.5				10.3
Lactic Acid	3.03				2.0

**Figure 1.** The patient initially arrived hemodynamically unstable with hypotension, bradycardia, and altered mental status. She received 3L of bolused IVF administration but vital signs remained refractory to treatment. After her ingestion of metoprolol was discovered, she received a bolus of glucagon and responded within minutes. She was presumed to be septic on arrival because of her leukocytosis, lactic acidosis, and right-sided pleural effusion (see figure 2). She also met 2 of 3 qSOFA criteria upon admission and continued to meet sepsis criteria even after appropriate IV fluid administration. Her vital signs stabilized only after glucagon administration which resolved her bradycardia, hypotension, altered mental status, leukocytosis and lactic acidosis.

\*Underlined values indicate qSOFA criteria being met with 2 or more criteria indication high mortality rate



**Figure 2.** The patient's chest x-ray showed right-sided pleural effusion (arrow) which was likely multifactorial from her history of smoking, alcohol use, and recent mitral valve repair. This was recurrent and incidental to her presentation. It was initially thought to be a sign of infection but fluid analysis later showed it to be transudative.



**Figure 3.** EKG on arrival showed bradycardia with HR of 57bpm on arrival. QRS interval was appropriately narrow at 90ms. QTc was also calculated to be mildly prolonged at 451ms.

## Treatment Guidelines

Mild cases of beta blocker overdose without severe bradycardia or hypotension may respond to atropine and IV fluid administration. More severe cases of beta blocker toxicity should be treated as follows:

1. The airway should be secured and advanced cardiac life support provided as necessary.
2. Up to two boluses of 3-5mg IV glucagon can be given 10 minutes apart. If the patient shows an improvement in heart rate or blood pressure, an IV glucagon drip should be started at a rate of 2-5mg/hr titrated to a goal of maintaining mean arterial pressure above 60mm Hg.
3. If the patient is refractory to glucagon, 1U/kg of regular insulin and 0.5g/kg can be bolused.
4. Seizures can result from beta blockers with high lipophilicity, most commonly seen with propranolol. Benzodiazepines should be given in the event of seizures.
5. Arrhythmias such as QRS widening and QTc prolongation can occur from beta blockers with membrane-stabilizing effects, which is also commonly seen with propranolol. Sodium bicarbonate should be given for QRS>120ms. Magnesium sulfate should be given for QTc>440ms.

## Discussion

Beta blockers as a class are one of the most commonly prescribed medications and subsequently one of the most common involved in overdose. Their main pharmacological target is antagonism of  $\beta_1$  and  $\beta_2$  receptors, which results in negative chronotropism and decreased blood pressure. However, certain beta blockers are more associated with overdose than others with propranolol being an order of magnitude more likely to cause toxicity. Propranolol is predisposed to ventricular arrhythmias and seizures because of its strong membrane-stabilizing effects and lipophilicity but these biochemical properties do not reliably predict toxicity. For example, carvedilol and propranolol both have membrane-stabilizing effects and are strongly lipophilic yet propranolol is 7.69 times more likely to be associated with fatal toxicity than its counterpart, carvedilol.

The non-specific effects of beta blocker toxicity can easily be mistaken for other pathology and this case study demonstrates how easily a patient can be misdiagnosed after acute ingestion of beta blockers. Our patient was initially presumed to be septic after presenting with hemodynamic instability, reactive leukocytosis, lactic acidosis from tissue hypoperfusion, and altered mental status from cerebral hypoperfusion and alcohol intoxication. She remained hemodynamically unstable despite appropriate IV fluid administration and only became hemodynamically stable after her acute beta blocker overdose was addressed.

In the setting of unstable vital signs and a questionable source of infection in a patient that is afebrile and bradycardic rather than tachycardic, a high degree of suspicion for beta blocker toxicity should be entertained. Beta blocker overdose will respond quickly to glucagon administration and this will prevent further complications and ultimately may be lifesaving.

## References

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