Chapter 19
Poisoning and Toxicity: The New Age

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Introduction

The approach to the hypotensive, bradycardic patient in the toxicologic setting can be complex, especially when the substance is unknown. The differential diagnosis is broad, but the approach to each patient remains the same.

Case Study

A 63-year-old female with a past medical history of hypertension, dementia, and depression presents to the emergency department with hypotension and bradycardia. The patient was "found down" outside her home by her husband who endorses that she has a history of suicide attempts in which

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she intentionally ingested several doses of her medications at once. He does not know her medications. Up until this point in time, the patient was in her usual state of health.

Vital Signs

BP: 70/40, HR 45, rr 15, and SpO2 96%
Fingerstick glucose: 200

Medications: unknown at this time
Past medical history: HTN, dementia, and depression
Past social history: previous history of recreational substance abuse
Past surgical history: none

Physical Exam

General appearance: somnolent, unable to answer questions, and minimally responsive to noxious stimuli.
Head: atraumatic and normocephalic.
Eyes: conjunctivae and corneas clear, 3 mm PERRL brisk, EOM's intact, and sclerae normal.
Ears: external inspection of the ears shows no abnormality.
Nose: normal.
Mouth: mucous membrane moist.
Neck: neck supple, no adenopathy, thyroid symmetric, normal size.
Heart: bradycardic rhythm, regular rate, no gallops, rubs, or murmurs.
Lungs: clear to auscultation and normal respiratory rate.
Abdomen: BS normal, abdomen soft, non-tender, no palpable bladder, no masses or organomegaly.
Skin: skin texture, turgor normal, no rashes or lesions, and axilla WNL.
Neuro: +2 patellar reflexes bilateral symmetrical, no clonus, and no rigidity.
Mental Status: unable to be assessed.
Musculoskeletal: no signs of trauma.

An EKG was obtained and is shown below (Fig. 19.1).

EKG

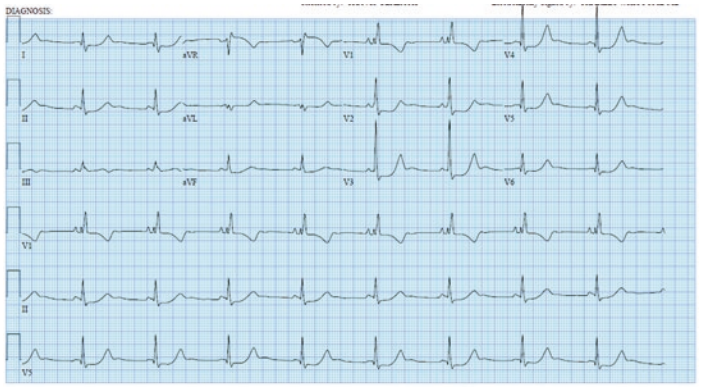

Figure 19.1 Sinus bradycardia 53, PR 108, QRS 116, QTc 493

Labwork

WBC 7.3, RBC 4.15, Hgb 12.8, and Hct 38.9
MCV 93.8
PLT 195

Na 128, K 4.9, Cl 110, and CO 20
BUN 15, Cr 1.38, and GFR 48
Glucose 141
Ca 8.6 and Mg 1.4

AST 204, ALT 162, and ALP 96
Protein 5.6, Tbili 0.8, and albumin 3.3
Lipase 45

Digoxin level undetectable

ABG 7.35/30/80/21 on RA

ETOH < 10
APAP < 10
ASA < 4

Urine Drug Screen:

Barbiturates: negative
Benzodiazepines: negative
Cocaine: negative
Opiates: negative
Amphetamine: negative

Toxicologic Differential Diagnosis of Hypotension and Bradycardia

1. Calcium channel blockers
2. Beta-blockers
3. Digoxin
4. Alpha-2 antagonists
5. Opiates
6. Sedative/hypnotics
7. Organophosphates/carbamates/cholinergic drugs

Calcium channel blockers (CCB) are classically divided into two major categories: dihydropyridines and nondihydropyridines. When evaluating an overdose, it can be important to recognize the subtle differences between the two. The nondihydropyridines, such as diltiazem and verapamil, block the myocardial and smooth muscle L-type calcium channels, leading to hypotension and bradycardia through vasodilation and impaired cardiac conduction. Dihydropyridines, such as amlodipine, felodipine, nicardipine, and nifedipine, preferentially block the L-type calcium channels in the vascular smooth muscle, which leads to vasodilation. However, unlike the nondihydropyridines, these drugs do not depress myocardial electrical conduction. Though uncommon, in the setting of an overdose and even at therapeutic doses, the vasodilation may lead to reflex tachycardia [1]. The key point here is that even if a patient presents with profound hypotension and tachycardia, the patient may still have taken a CCB. It is also important to note that many intentional ingestions involve more than one substance, which may alter a patient's "toxidrome," leading to a mixed clinical presentation.

Hyperglycemia may be noted on labwork. Insulin release is mediated by calcium entry into the pancreatic beta cells via L-type calcium channels. CCBs will not only target cardiac and smooth muscle but will also target the cells in the pancreas, blocking insulin release, ultimately leading to elevated blood glucose.

β-blockers (BB) act on the beta-receptors, preventing norepinephrine and epinephrine from binding to the receptor. This leads to decreased production of cAMP in the cardiac myocyte and limits the calcium influx through L-type calcium channels. As with CCBs, this results in myocardial depression and decreased cardiac contractility. Because of the pathophysiologic similarities to CCBs, a BB overdose is generally treated in the same way as a CCB overdose.

Of note, certain beta-blockers have additional concerns from a toxicologic standpoint.

Propranolol works through two different mechanisms: as a beta-receptor antagonist and as a membrane depressant via the sodium channel blockade. This can lead to ventricular tachyarrhythmias [2]. Propranolol is also known to be lipid soluble and can easily cross the blood-brain barrier, increasing risk for CNS depression and seizure [3].

Sotalol is a type III antiarrhythmic well established in literature to prolong the QT interval and can lead to torsades de pointes [4].

Hypoglycemia may or may not be observed in an overdose. It has been described in children and diabetics, though is less in adults. It is classically thought that hypoglycemia is facilitated through the blunting of sympathetic hypoglycemic symptoms, such as tremors, sweats, and tachycardia [5].

Digoxin

Digoxin is a cardiac glycoside that has been used in the treatment of atrial fibrillation and heart failure. It increases contractility by increasing cytosolic calcium. Digoxin and other cardiac glycosides bind and block the Na+/K+ ATPase

transporter on the extracellular membrane, leading to decreased Na + transport out of the cell and decreased K+ into the cell. The increased concentration of intracellular Na + allows for extracellular Na + to be pumped into the cell via the Na+/Ca2+ channel, while intracellular Ca2+ is pumped out. The increased calcium leads to further Ca2+ release from the sarcoplasmic reticulum during systole, increasing cardiac contractility.

It is worth noting that while we are discussing the hypotensive, bradycardic patient, digoxin toxicity can cause any type of change in both heart rate and cardiac rhythm. EKG findings can include PVCs, sinus bradycardia, atrial fibrillation, and ventricular tachycardias [6].

The clinical appearance of a patient with a digoxin overdose generally begins with GI symptoms – nausea, vomiting, and abdominal pain. Severe toxicity can lead to CNS symptoms – somnolence, confusion, lethargy, headache, and hallucination. Classically, patients have also described "yellow halos" in their fields of vision [7].

Potassium must be monitored in an overdose. As digoxin blocks the Na+/K+ pump, extracellular potassium increases. Hyperkalemia will further hyperpolarize myocardial conduction tissue and increases AV nodal block. The degree of hyperkalemia is a prognostic indicator of mortality [8].

In the undifferentiated hypotensive, bradycardic patient, a serum digoxin should be obtained; however, levels may be falsely elevated depending on when the last dose of digoxin was taken. After peak absorption, digoxin is then redistributed into the body stores. Blood concentrations taken prematurely (<6 h after last dose) are difficult to interpret and will not reflect complete redistribution levels. Because levels may be falsely elevated, it is important to assess how the patient clinically appears.

The indications for giving the antidote, digoxin-specific antibody fragments (digibind/digifab), are based on the patient's clinical picture and the following:

1. Cardiac arrest
2. Hemodynamic instability

3. Any life-threatening dysrhythmia
4. K+ > 5.0 in acute toxicity
5. Serum digoxin level > 10 nmol/L measured more than 6 h after ingestion in an acute ingestion regardless of symptoms
6. Acute ingestion of >10 mg in an adult (4 mg in a child)
7. Ingestion of non-pharmaceutical cardiac glycoside (e.g., as found in plants like foxglove and oleander, animals like the *Bufo* species toad, herbal preparations and traditional cultural medicines like *Chan Su*)

For elevated digoxin levels <10 nmol/L, treating with antidote must be weighed against the clinical picture and the patient's need for digoxin [9]. If the patient is not severely ill, ascertain why the patient was started on digoxin. Once the antidote has been given, digoxin levels can no longer be accurately measured until the digibind-digoxin complex has been eliminated. Digoxin assays are unable to accurately measure digoxin levels for 3 weeks, rendering it difficult to restart patient on therapy and properly dose the patient [10]. Also consider the high medical cost of the antidote.

Calculating the dose of digifab needed is unreliable if time of ingestion is unknown as measured serum digoxin level may not reflect the steady-state (postdistibutional) serum concentration.

Treatment is as follows [11]:

Acute toxicity:

- Known dose:
  - Dose (number of vials) = total ingested (mg) × 0.8 (bioavailability of tablet preparation) ÷ 0.5 of digitalis bound/vial
- Unknown dose:
  - Give five vials initially if the patient is hemodynamically stable
  - Give ten vials initially if the patient is hemodynamically unstable

- Repeat doses of five ampoules should be given every 30 min until reversal of digoxin toxicity is achieved
- In cardiac arrest give 20 vials (760 mg)

Chronic digoxin toxicity:

- Known level: number of vials required = (serum digoxin concentration – ng/L × (weight – kg) ÷ 100
- Empiric dosing: give one to three vials, can be re-dosed after 30 min and titrated to clinically effect.

Note that if a patient is ill due to ingestion of non-pharmaceutical cardiac glycoside (found in plants and animals), the digoxin level should not be used to estimate dosing. Treat with empiric dosing.

Alpha-2 Agonists

Clonidine, *tizanidine*, *guanfacine*, *methyldopa*, and *dexmedetomidine* are centrally acting alpha-2 adrenergic agonists. They reduce sympathetic outflow to the CNS, leading to a decrease in blood pressure, heart rate, and vascular tone. In an overdose, these agents can cause a prolonged CNS depression and, occasionally, hypothermia. Note that alpha agonism will lead to pinpoint/constricted pupils, often leading to the misdiagnosis of an opioid toxicity. Respiratory rate may be depressed, but unlike in an opiate toxicity, this generally responds well to external stimuli (auditory or tactile).

Naloxone has been used in high doses (4–10 mg) for reversal with variable response [12]. The mechanism behind increased blood pressure, heart rate, and level of arousal after naloxone is not well defined but is thought to relate to the modulation of CNS sympathetic outflow by endogenous CNS opioids [13].

The following substances may cause bradycardia and occasionally hypotension and can be peripherally regarded when thinking about the hypotensive, bradycardic patient. When considering the hypotensive, bradycardic patient, CCBs, BBs, alpha-2 agonists, and digoxin should be first on the differential diagnosis.

Opioids

Although uncommon, narcotics can cause varying degrees of hypotension (generally orthostatic) and bradycardia. *Methadone* in particular has been shown to have calcium channel antagonism [14, 15].

Sedative/Hypnotics

Benzodiazepines, *barbiturates*, *baclofen*, *GHB*, *sodium oxybate*, *and carisoprodol (SOMA)* are all examples of sedative-hypnotics that can lead to hypotension and bradycardia.

Though their exact mechanisms vary, simplistically, these medications involve agonism of the GABA-A or GABA-B receptor and can clinically present as decreased mental status, respiratory depression, and bradycardia.

Flumazenil has been used for iatrogenic and pediatric benzodiazepine overdoses. It is generally not recommended to give flumazenil in an adult who potentially is benzodiazepine-dependent due to the precipitation of withdrawal. Benzodiazepine withdrawal is not benign and can lead to seizures, hypertension, tachycardia, hallucinations, psychosis, and coma. Once flumazenil is administered, the specific binding site for benzodiazepines is blocked. Should the patient experience seizures, the patient will not be able to respond to benzodiazepines [16]. It is worth noting that barbiturates, while also GABA-A agonists, bind to a separate site on the GABA receptor and could potentially be used in a seizing patient unresponsive to benzodiazepines.

GHB is a GABA-B agonist that has historically been abused by bodybuilders for its supposed anabolic properties. It is also known to be used as a recreational substance or for facilitation of physical/sexual assault. Ingestion can cause deep sedation, bradycardia, and coma, sometimes requiring intubation. The classic presentation is of a patient who presents comatose and is intubated for airway protection. Ninety minutes later, the patient abruptly awakens and self-extubates [17].

Organophosphates/Carbamates

Organophosphates and carbamates are compounds often found in insecticides and agents of warfare.

In the body, acetylcholine is a neurotransmitter that functions in multiple ways. It is used at the neuromuscular junction to activate skeletal muscles, used as a neurotransmitter in the autonomic nervous system, and also used as a neurotransmitter in the CNS in both the parasympathetic and sympathetic nervous system.

Organophosphates and carbamates inhibit the enzyme cholinesterase, which is the enzyme breakdown acetylcholine. This leads to an excess of acetylcholine at nerve synapses and neuromuscular junctions, which results in overexcitation of acetylcholine receptors. This is better known as a cholinergic crisis, which can manifest as nausea, headache, shortness of breath, rhinorrhea, salivation, diaphoresis, confusion, bronchorrhea, muscle fasciculations, seizure, diarrhea, paralysis, and coma.

Because acetylcholine functions as a neurotransmitter for both the sympathetic and parasympathetic nervous systems, a patient with a severe overdose may present with autonomic instability. Parasympathetic stimulation commonly predominates, which manifests as hypotension, bradycardia, and miosis. A patient may have a mixed picture as the sympathetic stimulation leads to tachycardia, hypertension, and mydriasis [18].

There are also *cholinergic agents* to keep in mind, such as *donezepil (Aricept)*, *physostigmine*, *neostigmine*, *rivastigmine*, *and galantamine*.

Depending on type and route of exposure, treatment involves decontamination (skin and mucous membranes) and provider protection with chemical-protective clothing.

Atropine addresses the life-threatening muscarinic symptoms including bradycardia, hypotension, bronchorrhea, and bronchospasm. It should be given in escalating doses, starting at 2–5 mg IV, and titrated every 5–10 min until patient's secretions and clinical picture improve.

Pralidoxime is used in the setting of an organophosphate (OP) overdose to reactivate cholinesterase enzymes; however, based on route of exposure, type of OP (some organophosphates may quickly irreversibly bind to cholinesterase), this may or may not be helpful in an overdose. It is most helpful in an OP overdose when given as early as possible. It is not typically given with carbamates.

Pralidoxime should be given as a loading dose (30–50 mg/kg, total of 1–2 g in adults) over 30 min, followed by a continuous infusion of 8–20 mg/kg/h (up to 650 mg/h) [19].

Plants, Herbs, and Animals

As providers are exposed to different cultures, it is worth briefly noting that there are many plants (e.g., oleander, foxglove), traditional medicinal preparations (e.g., aconite in Chinese herbal preparations), and diet (e.g., shellfish poisoning/toxic fish poisonings) that can cause hypotension and bradycardia [20, 21]. Obtaining a comprehensive history may be crucial to identifying the patient's source of exposure once the patient has been stabilized.

Management of the Acutely Ill, Hypotensive, Bradycardic Patient

1. Establish and *maintain the patient's airway*.
2. Place patient on *cardiac monitor* and place *pacer pads*.
3. Obtain adequate *intravenous access*. Establish central access if anticipating need for multiple pressors, large amounts of fluid, and high concentration solutions like D20W.
4. Send CBC, BMP, LFTs, ETOH, ASA, and APAP. If undifferentiated, it is reasonable to add a digoxin level.
5. If patient presents within *1–2 h after ingestion*, consider aggressive *early decontamination*. For example, in the

case of CCB/BB overdose, the severity of toxicity can be profound, and the benefit to decontamination is great:

(a) If the patient is *alert* and able to maintain an airway, consider giving *activated charcoal*.
(b) If patient is *intubated*, consider giving *activated charcoal and performing gastric lavage.*
(c) If the patient has taken sustained release tablets or if bezoar formation is suspected, whole bowel irrigation may also be considered. Note that a negative CT does not rule out a bezoar [22].

6. Assess volume status:

(a) Bedside US can be utilized to assess ejection fraction, ventricular wall movement, and IVC collapsibility.
(b) Give *IV fluid bolus in the absence of fluid overload*.

7. *Atropine*

(a) Inhibits the effects of vagal stimulation, which can temporarily reverse AV nodal blocks, leading to an increased electrical conduction and increased heart rate.
(b) Given the relative ease of access to atropine, it is a reasonable medication to try. In severe antihypertensive overdose, however, it is usually not successful.
(c) *Dose: 0.5 mg–1 mg IV q 3–5 min; max 3 mg total.*

8. *Intravenous calcium*

(a) If the patient is known to have taken a CCB, the theory behind giving intravenous calcium is competitive antagonism and peripheral vascoconstriction. Note that calcium chloride contains three times the amount and has potential to be venosclerotic.
(b) If the patient is known to have taken digoxin, it may be prudent to avoid giving calcium; however, this stems from older animal models that showed an increase in digoxin toxicity when calcium was given.

The theory behind this being calcium may lead to an irreversible noncontractile state, due to impaired diastolic relaxation from calcium-troponin C binding. The human evidence for developing cardiac tetany or a "stone heart" is poor [23]. IV calcium should not be withheld from a critical patient if it may prove beneficial.

(c) *Dose: calcium chloride 1 g IV or calcium gluconate 3 g IV with goal serum calcium 12-13 mg/dL.*

9. *Pressors*

   (a) *Norepinephrine/epinephrine*

   - In regard to *dopamine*: dopamine receptor selectivity is poor, and its mechanism of action is indirect and less predictable than that of norepinephrine. Dopamine preferentially binds to dopamine receptors which may cause hypotension at low doses. It then converted to NE and stimulates the release of NE. If a patient is already on NE, adding dopamine does not necessarily confer increased pressor support. Additionally, the 2016 Cochrane review of vasopressors for hypotensive shock noted increased arrhythmogenicity with dopamine.

   (b) *Vasopressin* does not act on adrenergic receptors and may be added if there is no response to norepinephrine/epinephrine.

   (c) In a patient with poor cardiac contractility, also consider dobutamine and phosphodiesterase III inhibitors (inamrinone, milrinone, and enoximone).

10. Give *antidote* if indicated

   (a) *Digifab* for digoxin (see above digoxin section for dosing)

   (b) *Naloxone*

   - 4–10 mg IV for clonidine

11. *Glucagon*
    (a) A reasonable therapy to start, especially if suspecting a beta-blocker overdose.
    (b) Glucagon stimulates adenyl cyclase via G proteins, resulting in increased intracellular cyclic AMP which in turn leads to stimulation of muscle contraction, resulting in positive inotropic and chronotropic effects, similar to beta-agonists [24].
    (c) *Dose: 5–10 mg IV bolus and watch for response within 5 min.* Glucagon may be re-dosed. If clinical response is noted, patient should immediately be started on a *glucagon infusion at response dose per hour.*
    (d) Note that glucagon may cause nausea and emesis, which may compromise the patient's airway.
12. *High-dose insulin euglycemia therapy (HIET)*
    (a) Pathophysiology
        - The myocardium uses free fatty acids for energy but in a shock state will use insulin. In a CCB overdose, patients become hyperglycemic and insulin resistant. The heart enters a metabolic stress state but is unable to utilize glucose. Without the needed energy, myocardial depression and hypotension ensue [25]. HIET promotes uptake of glucose and facilitates oxidation and clearance of metabolic "stress state" by-products, including lactic acid and end products of glycolysis [26].
        - Insulin has also been shown to provide inotropy as demonstrated in animal studies [27].
    (b) Labwork
        - Frequent glucose checks are necessary, and serial electrolytes need to be monitored. Hypokalemia due to insulin-mediated intracellular shifting can be supplemented with IV potassium; however, it is important to remember that patient's total body

potassium is not depleted. When HIE is stopped, potassium will shift out of the cells.

(c) *Dosing*

- Start insulin as soon as possible as it will take time to see clinical effect (approximately 20–30 min). Bridge with pressors as needed.
- *Bolus 1 IU/kg insulin with or without 25 g dextrose bolus*

  1. Avoid insulin bolus if glucose <150
  2. Avoid dextrose bolus if glucose >400

- *Start 1–2 IU/kg/h drip with goal blood glucose of 100–250*

  1. Perform glucose checks q30 minutes until blood glucose is stable, and then space to 1–2 h
  2. Check potassium levels q1 hour, and replete when K < 2.5 mEq/L

(d) Goals of treatment

- Therapy should be guided by patient's hemodynamic status. A *HR > 50 and MAP > 65* is a reasonable goal.
- HIET is stopped after vasopressors have been weaned. The approach to cessation of HIET is not well defined as some physicians advocate a slow taper, while others advocate for abruptly cessation to allow for self-tapering of insulin from insulin release of body lipid stores [28].
- We recommend weaning insulin infusion 0.5 U/kg/h every 2–4 h once vasopressors have been stopped. Closely monitor glucose and electrolytes during the weaning process and for 24 h after discontinuation of insulin infusion.

If the above steps have not led to adequate control of the patient's clinical presentation, consider the following:

13. Other pressors
    (a) Methylene blue
        - The suspected mechanism of action of methylene blue is inhibition of the enzyme nitric oxide synthase, which ultimately prevents the smooth muscle dilation [29].
        - This will turn the patient blue and will interfere with colorimetric lab testing like CO-oximetry and also lead to inaccurate readings on pulse oximeter [30].
    (b) Hydroxocobalamin
        - The suspected mechanism of action is the sequestration and subsequent depletion of nitric oxide in vascular endothelium preventing vasodilation [31].
        - It changes colors of body fluid to a dark-wine color, which can interfere with colorimetric methods used in laboratory measurements such as aspartate aminotransferase, total bilirubin, creatinine, magnesium, and serum iron [32]. It also may interfere with CO-oximetry testing of carboxyhemoglobin, methemoglobin, and oxyhemoglobin.
        - Depending on the hemodialysis machine, hydroxocobalamin may trigger the blood leak alarm on a dialysis circuit due to its color. When it crosses the semipermeable membrane, some machines have been known to terminate dialysis because it interprets the presence of hydroxocobalamin as in the dialysate [33].
14. *Lipid emulsion therapy*
    (a) The exact mechanism for intralipid therapy is not completely understood, but it is thought that once intralipid is circulation, the emulsion extracts lipophilic drugs, preventing them from distributing into the serum [34]. The evidence of lipid emulsion therapy comes from the treatment of local anesthetics,

such as lidocaine and bupivacaine; however, further investigation is underway to assess benefit in other lipophilic medications.

(b) Medications that are thought to have had some benefit include amlodipine, verapamil, bupropion, carvedilol, cyclic antidepressants, diphenhydramine, flecainide, metoprolol, organophosphates, propranolol, quetiapine, and timolol [35, 36].

(c) *Pitfall:* It is important to draw labs such as ABG, CBC, electrolytes, triglycerides, and serum drug concentrations prior to dosing as intralipid will interfere with these lab tests once administered.

(d) *Note:* It is contraindicated in use in patients with severe egg or soybean allergy.

(e) Using intralipid is not without risk:

- Hypertriglyceridemia, acute pancreatitis, cholestasis, and increased risk of infection have been described [37].
- Fat overload syndrome is a well-known complication of intravenous lipid emulsion therapy, directly relating to the rate of administration of infusion. As this is a relatively novel therapy, the upper limits of infusion rates and dose are not defined. The syndrome is characterized by headaches, fever, anemia, jaundice, hepatosplenomegaly, respiratory distress, ARDS, and DIC [38].

(f) *Dose: 1.5 mL/kg as an initial bolus followed by 0.25 mL/kg/min for 30–60 min.*

(g) If considering extracorporeal membrane oxygenation (ECMO), note that intralipid may potentially create problems, including clogging and cracking in an ECMO circuit [39]. To this point, if a patient is already actively receiving ECMO, it may not be salient to start intralipid. Conversely, failed intralipid therapy should not stop a provider from starting ECMO.

15. Nonpharmacologic therapies [40]

(a) Temporary cardiac pacing can be considered but usually unsuccessful in treating the severely ill, poisoned patient.
(b) *Dialysis:* antihypertensive agents are poorly dialyzed, though some studies have shown that atenolol, acebutolol, and sotalol may have some clearance through dialysis [41]. This may or may not translate to better clinical outcomes and should only be considered if pharmacologic therapies have been exhausted.
(c) *Intra-aortic balloon pump/left ventricular assist device/VA ECMO*

- Mobilize these therapies early if the patient is severely ill.

Case Conclusion

The patient's husband was able to find his wife's medication list, which included diltiazem. The patient received IV fluids, atropine, pressors, and glucagon (with no effect) and ultimately was placed on HIET with full recovery.

Key Points

- The undifferentiated toxicologic hypotensive bradycardic patient has a wide differential diagnosis. Obtaining a comprehensive history is important and may help further guide management, but in the critically ill patient, starting the algorithm may help attain hemodynamic stability.
- Given the elevated morbidity and mortality of calcium channel and beta-blocker overdoses, consider early aggressive decontamination.
- In the undifferentiated patient, a digoxin level should strongly be considered.

- Not all calcium channel blockers and beta-blockers are equivalent. In addition to hypotension and bradycardia, consider seizures and tachyarrhythmias in propranolol; consider QTc prolongation in sotalol.
- In a severely ill patient, a single agent is not likely to help. Starting multiple therapies, e.g., IV fluids + IV calcium + pressors + glucagon + high-dose insulin, is more likely to be successful in stabilizing the patient.
- Insulin *needs* to be started at and is most effective at high doses (1–2 IU/kg) with frequent monitoring of electrolytes and glucose.
- Consider intralipid therapy if all other pharmacologic therapies have failed.
- Mobilize dialysis/IABP/LVAD/VA ECMO early in a critical patient.

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