CSI-TOX Case 1

CASE HISTORY:

A 45-year-old woman presents to the emergency department by EMS for altered mentation. She was last seen by family the night before and was known to have had an argument with her boyfriend. Her oldest daughter found her after becoming concerned when her phone calls went unanswered. The daughter described the patient as difficult to arouse with sonorous respirations. The patient has a known history of hypertension but no other past medical conditions and no history of illicit drug use. Upon arrival she is bradycardic, hypotensive, and sedated with intermittent deep, sighing respirations. Her gag reflex is intact. She becomes agitated at times and withdraws to the pain of the IV being started. Naloxone 0.4 mg IV once was given without response.

PMHx: Hypertension
Meds: Unknown
SurgHx: Cholecystectomy
Allergies: PCN
SocHx: Divorced, works on assembly line at a local factory, smokes tobacco, no alcohol, or illicit drugs.

PHYSICAL EXAM

BP-90/56 mm of Hg, HR-54 bpm, RR-8/min, T-96 F, and SpO2-91% RA

General: Comatose, unresponsive to verbal. Localizes painful stimuli.
   Eyes remain closed
HEENT: Pupils 2 mm, sluggish to light; mucous membranes moist
Neck: Supple with no abnormalities
Chest: Clear to auscultation bilaterally with good air entry on bag valve respirations
Cardiac: Bradycardic; S1, S2 noted; regular rhythm, no abnormal heart sounds
Abdomen: Soft; bowel sounds normal; no liver or spleen enlargement
Rectal: Decreased tone; brown, guaiac negative stool
Skin: No rashes or lesions; no trauma
Musculoskeletal: No edema; no acute trauma, no joint swelling
Neurologic: Somnolent, with poor muscle tone. Intermittent agitation with tactile stimulation. DTRs diminished throughout, no clonus, plantar reflexes equivocal, no facial asymmetry, pupils 2 mm, gag reflex intact

LABS

ABG: 7.34/48/260/26.8/100%, FiO₂ = 0.5
Na 138 mmol/L, K 3.8 mmol/L, Cl 102 mmol/L, bicarb 22 mmol/L, BUN 15 mg/dl,
Cr 1.2 mg/dl, glucose 113 mg/dl, WBC 9000 cells/mcL, Hct 38.4%, Plt 338,000/mcL
Urine analysis unremarkable, Urine drugs of abuse screen negative, serum ethanol undetectable
ECG: Sinus bradycardia, HR 50 bpm, QRS 82 ms, QTc 430 ms

QUESTIONS

1. What is your differential for patients presenting with bradycardia and hypotension?

There are a number of medical conditions that can result in this combination, but bradycardia in the setting of hypotension should alert you to possible drug toxicity. There are a large number of medications that cause hypotension both directly and indirectly. Indirectly, a patient may develop hypoxia, acidemia, or volume depletion that will lead to hypotension. Direct causes of hypotension are either the result of increased venous capacitance through reduced vascular tone or from negative inotropic effects causing myocardial depression. Vasodilation is typically mediated through b₂-adrenergic agonism or alpha₁-adrenergic antagonism. Sedatives and drugs with imidazoline or a₂-adrenergic agonist properties result in decreased sympathetic outflow from the central nervous system and subsequent hypotension. Finally, some medications will deplete stores of catecholamines, resulting in the reduction in vascular tone. Although there are a number of medications producing the above effects, many of them do not blunt the physiological response to hypotension: i.e., tachycardia. Commonly encountered medications that result in hypotension and bradycardia can be summarized by the mnemonic “ABCDs”:

- Alpha₂ agonists (clonidine, tizanidine, etc.) and Antidysrhythmics
- Beta blockers
• Calcium channel antagonists
• Digoxin (and other cardiac glycosides)
• Sedatives, Severe opioid overdose

2. List the drugs that classically cause sedation with miosis?

Miosis is an easily recognized sign in overdose and can be very helpful in the setting of drug overdoses. That being said, sedated patients with predominating parasympathetic drive will have a reduction in pupil size. Severely constricted pupils can still serve as a diagnostic clue. The more commonly encountered classes of drugs/toxins causing miosis include atypical antipsychotics, cholinergic compounds, clonidine, opioids, phencyclidine, and the phenothiazines. Not all of these exposures result in sedation, however. Olanzapine, clonidine, opioids, and phenothiazines (such as prochlorperazine) will often result in sedation with miosis.

3. The paramedics tell you that they found an empty bottle of clonidine 0.1 mg next to the patient at home. Is her presentation consistent with a clonidine overdose?

Yes. Clonidine intoxication primarily involves the central nervous system (CNS) and cardiovascular system. Classically, patients present with miosis, bradycardia, CNS depression, transient early hypertension followed by hypotension. Patients may become irritable or agitated in response to tactile stimulation. Other CNS effects include hypotonia, hyporeflexia, hypothermia, miosis, and seizures (rare). Symptoms typically occur early, within 6 hours following ingestion and resolve over 12-36 hours.

The cardiovascular effects following clonidine overdose include early transient hypertension likely from agonism of peripheral postsynaptic $a_2$-adrenergic receptors producing vasoconstriction. This is typically short-lived and followed by hypotension and bradycardia. Bradycardia is typically sinus in nature but there are several case reports of AV blocks (Wenckebach and complete heart blocks) or junctional rhythms. Significant dysrhythmias are not expected and should prompts investigation for possible co-ingestants. Although there are several cases of patients developing dysrhythmias reported in the literature, these cases are uncommon and often clouded by multiple other co-ingestants, such as digoxin.

Hypotension is likely due to a combination of a centrally mediated reduction in sympathetic outflow as well as depletion of circulating norepinephrine (NE). In controlled setting, hypotension occurs when clonidine levels are > 2 ng/mL, suggesting a dose dependent relationship of clonidine and hypotension.
4. What is the mechanism of action of clonidine?

Clonidine is an imidazoline-based direct acting $a_2$-adrenergic agonist. Clonidine lowers blood pressure through several mechanisms both centrally and peripherally, although not all these pathways are entirely understood. It acts by binding to both $a_2$-adrenergic and imidazoline binding sites. Three highly homologous $a_2$-adrenergic receptor subtypes exist as $a_{2A}$, $a_{2B}$, and $a_{2C}$. They are both presynaptic and postsynaptic and exist centrally and peripherally. Central $a_2$-adrenergic receptors inhibit the release of NE and acetylcholine (postganglionic). Postsynaptic $a_2$-adrenergic receptors inhibit adenylate cyclase and lower cAMP levels. These actions occur primarily in the nucleus tract solitarius and locus ceruleus, resulting in sedation and reduction in blood pressure and heart rate. Peripheral $a_2$-adrenergic receptors mediate vasoconstriction similar to that seen with peripheral $a_1$-adrenergic receptors. Clonidine is not a selective central versus peripheral agonist and therefore both central and peripheral effects are expected to occur with exposure.

5. List other agents with the same mechanism of action to clonidine that would be expected to produce similar clinical manifestations?

Other commonly encountered imidazoline-type drugs with a similar overdose toxidrome include clonidine, brimonidine (Alphagan®), tetrahydrozoline (Visine®), naphazoline (Vasoclear®), xylometazoline (Otrivin®), tizanidine (Zanaflex®) and oxymetazoline (Afrin®).

6. When do you expect patients to develop symptoms from acute clonidine ingestions?

Clonidine is well absorbed orally with a 100% bioavailability. Peak plasma concentrations occur 1-3 hours after ingestion. The initial manifestation of overdose is mental status changes and usually occurs within an hour. Hypotension and bradycardia generally occur several hours later.

7. What is the role of naloxone in acute clonidine toxicity?

The constellation of symptoms of CNS depression, miosis, and hypotension resemble opioid toxicity and may lead physicians to treat clonidine overdoses with naloxone.
Naloxone’s mechanism of action in the reversal of both CNS depression and hypotension is poorly understood. Due to similar cell signaling pathways, opiate receptor antagonism (with naloxone) may mimic the reversal of central $a_2$-adrenergic receptor activation. Additionally, hemodynamic improvement may be due to naloxone countering the inhibition of norepinephine release that is thought to be associated with opiate receptor activation.

8. How would you treat this patient?

Supportive care. Activated charcoal may be considered but administration may be limited due to the risk of aspiration from early onset of CNS depression. This patient needs her airway, breathing, and circulation assessed frequently. Continued, intermittent stimulation may improve symptoms and prevent the need for mechanical ventilation. Hypotension and bradycardia often respond to IV fluids and atropine, respectively. Refractory hypotension unresponsive to crystalloids can be treated with epinephrine or dopamine. Symptomatic patients require admission to an intensive care unit. Symptoms typically resolve in 12-36 hours.

BONUS

1. What was the original intended use for clonidine?

Nasal decongestant. In 1962 clonidine demonstrated an ability to cause vasoconstriction of blood vessels in the nasal mucosa. Note that this feature is common among the imidazoline drugs such as oxymetazoline (Afrin®).