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ABCs of CCBs

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Cardiovascular medications are a leading cause of death from drug exposures. What steps can be taken in the ED to prevent fatality? Find out in this case of a woman who took undetermined quantities of several agents.

Case

A 69-year-old woman with a history of hypertension and depression presents to the emergency department after ingesting unknown quantities of amlodipine, atenolol, and thioridazine 3 to 5 hours earlier. The patient's vital signs are as follows: blood pressure (BP), 135/62 mm Hg; heart rate, 50 beats/min; respiratory rate, 18 breaths/min; temperature, 97.9°F. Her oxygen saturation is 95% on room air, and her blood glucose level is 181 mg/dL. Other examination findings are unremarkable, except for lethargy. One hour after her initial presentation, a repeat BP is 67/40 mm Hg and her heart rate is 44 beats/min. The ECG shows normal sinus rhythm.

Are all calcium channel blockers the same?

In 2010, cardiovascular drugs were the fifth leading class of drugs associated with referrals to poison control centers and the second leading drug exposure–related cause of death in adults (following analgesics), with 128 reported fatalities.[1] Calcium channel blockers (CCBs) were responsible for 40% of all cardiovascular drug–associated fatalities, followed by β-blockers and cardioactive steroids (such as digoxin).[1] Among the CCBs, amlodipine was responsible for the largest number of fatalities (24), followed by diltiazem and verapamil. This is quite distinct from just a decade ago, when the majority of CCB overdose fatalities were due to verapamil and diltiazem.[2]

There are three classes of CCBs: dihydropyridines (eg, nifedipine and amlodipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem). The nondihydropyridines—verapamil and diltiazem—bind to the L-type calcium channels in the myocardium, nodal tissue (sinoatrial and atrioventricular nodes), and vascular smooth muscles. Verapamil has the most potent effect on the myocardium, followed by diltiazem. In contrast, dihydropyridines bind calcium channels preferentially in vascular smooth muscle due to their enhanced binding at less negative membrane potentials: the resting potential for smooth muscle is −70 mV versus −90 mV for myocardium.[3] Thus, they are potent peripheral vasodilators and have limited effect on the myocardium even following substantial overdose. This likely accounts for their relative safety in overdose, despite the apparently paradoxical prior statement about their increasing involvement in poisoning deaths.

What are the expected clinical findings in CCB overdose? How can one differentiate CCB overdose from β-blocker overdose?

Patients with CCB or β-blocker overdose may initially be deceivingly asymptomatic and hemodynamically stable. However, immediate attention is critical, as car-

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diovascular collapse can develop rapidly. In general, patients who ingest immediate-release formulations develop clinical signs within 2 hours, whereas the onset of toxicity can be delayed for 6 hours, or even longer, with exposure to sustained-released formulations.

Patients with dihydropyridine CCB overdose typically develop profound hypotension with a prominent reflex tachycardia, and this latter finding clearly distinguishes this class of CCBs from the nondihydropyridines. Despite impressive vital sign abnormalities (hypotension and bradycardia), particularly with verapamil or diltiazem, patients may maintain an alert mental status. This is postulated to be related to inhibition of the neuronal calcium ion entry that causes neuronal dysfunction.[4]

β-Blockers tend to produce less prominent vital sign abnormalities but are associated with altered mental status (since they do not block neuronal calcium channels). In most healthy people at rest, the cardiovascular effects of a therapeutic dose of a conventional β-blocker, such as metoprolol, are minimal. Only with cardiovascular stress, such as with exercise or anxiety, does the β-blocker's ability to block endogenous sympathetic stimulation manifest (as a lack of tachycardia).

Due to different effects on pancreatic release of insulin, CCBs, regardless of class, typically cause hyperglycemia in overdose, while β-blockers cause hypoglycemia, albeit less predictably. Diverse ECG changes can occur following overdose with either CCBs or β-blockers and do not help differentiate between the two types of agents. However, the dihydropyridines generally produce only sinus tachycardia and have little direct myocardial effect.

What are the initial steps in managing a patient with a mixed β-blocker/CBB overdose?

Following the initial assessment and implementation of standard supportive care, the need for gastrointestinal decontamination should be considered. Most awake and clinically stable patients should receive activated charcoal at a dose of 1 g/kg orally. Whole bowel irrigation (WBI) with polyethylene glycol solution (1 to 2 L/h orally) should generally be used in patients who ingest sustained-released β-blockers or CCBs. By enhancing gastrointestinal elimination of sustained-release agents, WBI can decrease the enteric absorption of the drug. Both activated charcoal and WBI should be deferred in patients with decreased gastric motility or hemodynamic instability.[5]

Patients with hypotension who fail to respond to intravenous saline should receive intravenous calcium salts to increase the Ca^{2+} concentration external to the blocked calcium channel. Calcium administration improves cardiac inotropy and electrical conduction and improves hypotension in patients with both β-blocker and CCB poisoning; for the latter, calcium is an essential antidote. However, this effect is short-lived due to the rapid dissipation of this enhanced transmembrane Ca^{2+} concentration gradient. Thus, repeat bolus dosing may be required. Although calcium chloride contains three times more calcium ion than calcium gluconate (13.4 vs 4.3 mEq in a standard 10-mL dose), the latter is generally used due to safety considerations. The recommended initial bolus dose is 30 mL IV of 10% calcium gluconate (or 10 mL of 10% calcium chloride). This bolus can be repeated every 15 to 20 minutes as needed, up to three to four doses, without concern for systemic hypercalcemia.

Inotropes target the β_1-adrenergic receptors in the myocardium, while vasopressors bind to the α_1-adrenergic receptors in the peripheral vascular smooth muscle. Among the available inotropic and vasopressor agents, norepinephrine is preferred due to its direct action on the adrenergic receptors. Dopamine, an agent that stimulates norepinephrine release, has unpredictable effects in a severely poisoned patient and is best avoided. Vasopressin works via G protein–coupled V_1 receptors in the peripheral vasculature, with minimum effect on inotropy. In theory, vasopressin may be useful in reversing the peripheral effects of dihydropyridine toxicity, but the clinical evidence is limited.

Glucagon is the initial therapy of choice in patients with β-blocker poisoning.[6] Glucagon increases inotropy (more than chronotropy) by increasing cAMP (cyclic adenosine monophosphate) formation by adenylate

cyclase. This activation occurs via glucagon receptors independently of the β-adrenergic receptors that are blocked by the β-blockers. In this manner, glucagon functions like a β_1-agonist. Its benefit in patients with CCB overdose is probably no greater than that noted with standard pressors/inotropes, such as norepinephrine, since the effects of CCBs occur downstream of the adenylate cyclase cascade. An initial dose of 3 to 5 mg IV given slowly over 1 to 2 minutes can be titrated as needed to a maximum single dose of 10 mg[7]; a maintenance infusion of 2 to 5 mg/h may be used subsequently if there is a beneficial response. An important concern with glucagon is the risk of vomiting, which raises the risk of aspiration, and bradycardia due to increased vagal tone. For this reason, since the β-adrenergic receptor is available in patients with CCB overdose, norepinephrine is preferable in these patients.

What is hyperinsulinemia/euglycemia therapy, and when is it appropriate?

In the setting of severe CCB poisoning in which the above interventions have failed, hyperinsulinemia/euglycemia (HIE) therapy, ie, high-dose insulin with dextrose supplementation, has become the preferred therapeutic intervention. Under normal conditions, myocardial tissues preferentially use free fatty acids as their source of energy. However, myocardial metabolism shifts to a glucose-dependent process under stressed conditions (eg, cardiovascular collapse).[8] For this reason (and likely for other reasons), HIE enhances inotropy in the setting of both CCB and β-blocker poisoning. Although there are no randomized controlled clinical trials of HIE therapy, animal studies and human case reports suggest it is effective in restoring the hemodynamic status of patients with severe nondihydropyridine (verapamil) toxicity.[9] However, evidence of clinical benefit in the setting of dihydropyridine toxicity is more limited. This seems understandable since with dihydropyridine poisoning the main toxicologic effect occurs in the peripheral vasculature instead of the myocardium. It should be noted that there is generally a delay in the onset of action of HIE therapy of approximately 15 to 60 minutes.[10]

An initial insulin bolus of 1 to 2 units/kg IV is immediately followed by continuous infusion of 0.5 to 1 unit/kg/h. The continuous infusion can be increased by 1 unit/kg/h every 15 to 30 minutes and titrated to achieve the desired hemodynamic response. The upper limit of the continuous infusion has not been clearly defined. The common side effects of HIE are hypoglycemia and hypokalemia. Interestingly, the hypoglycemia is not as profound and difficult to prevent as might be expected, an effect likely related to saturation of peripheral insulin receptors.[10] Regardless, the patient's blood glucose and potassium must be closely monitored.

Case Conclusion

Glucagon and calcium gluconate were administered with no hemodynamic improvement. Due to deterioration of her mental status, the patient was intubated for airway protection. She was started on norepinephrine for persistent hypotension (systolic BP, 85 mm Hg) and, despite the addition of vasopressin, remained hypotensive. HIE therapy, bolus plus infusion, allowed downward titration of the pressor agent. Over the next hour, the patient's BP stabilized to 115/62 mm Hg, and all therapy was discontinued over the next 16 hours. The patient fully recovered without any further complications. **EM**

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