Amlodipine poisoning management

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Amlodipine is a commonly used calcium-channel blocker (CCB) used in the treatment of hypertension. Severe CCB toxicity is highly lethal, as a result of cardiovascular collapse. Amlodipine overdose can lead to prolonged hypotension and potent vasodilatation which can result in fatality. Early identification of CCB overdose can save lives and reduce the risk of complications. The management of CCB intoxication will be reviewed.

Keywords: amlodipine overdose, calcium-channel blockers toxicity, high-dose insulin euglycaemic therapy (HIET), lipid emulsion therapy, hypotension

Introduction

The CCBs have different effects on the cardiac rate, contractility and heart conduction and therefore are divided into two major categories based upon their predominant physiological effects: dihydropyridines (amlodipine, felodipine, nifedipine, lercanidipine) and non-dihydropyridines (verapamil, diltiazem). The dihydropyridines preferentially affect vascular smooth muscle, thereby decreasing peripheral vascular resistance, reducing afterload and lowering blood pressure. They are therefore used in the management of hypertension and angina pectoris.1 The non-dihydropyridines have more significant myocardial effects thereby decreasing conduction and heart rate. They are therefore preferentially used in supraventricular arrhythmias and angina including Prinzmetal’s angina.2 However, in overdose, receptor selectivity may be lost, so even dihydropyridines may cause cardiotoxicity in addition to vasodilation in large overdoses.3

CCBs act by reducing calcium ion entry via the voltage gated L type calcium channels thus reducing release of calcium from the sarcoplasmic reticulum and thereby reducing contractility of myocardial and vascular smooth muscle.4,5 Calcium channels are functionally important not only in cardiac myocytes and vascular smooth muscle cells but also in islet beta cells of the pancreas, the central nervous system and skeletal muscle.1 Therefore blockade of calcium channels in the pancreatic beta cells can cause reduced insulin release.1,4

Ingestion of excessive CCBs, either accidental or in deliberate self-harm, is one of the most potentially lethal drug overdoses.1 The exact toxic dose has not been fully established, however it is recommended that adult patients be monitored for toxicity if more than 10 mg amlodipine was ingested (> 0.3 mg/kg in children).1 Verapamil and diltiazem are the most lethal CCBs in overdose and the patient should be monitored if more than 120 mg verapamil immediate-release or more than 480 mg verapamil sustained-release (> 2.5 mg/kg in children) was ingested.6

Pharmacokinetics

All subtypes of CCBs are very well absorbed orally, undergo extensive hepatic first-pass metabolism (metabolised by cytochrome P450 system). CCBs are lipophilic, bind highly to plasma proteins and have a large volume of distribution (> 2 liters/kg) so elimination by haemodialysis or haemofiltration is ineffective.7,8 They are excreted mostly in the urine. At higher doses, clearance slows, because hepatic clearance changes from first-order to zero-order kinetics. Amlodipine has an elimination half-life of approximately 30 to 50 hours while verapamil’s half-life is shorter up to eight hours (up to 12 hours in repeated doses).9,10

Diagnosis of the overdose

The diagnosis of CCB poisoning is made clinically on the basis of the history and clinical findings. Typically there is a history of overdose combined with hypotension. Patients may maintain a clear mental status despite hypotension and bradycardia. Patients with significant CCB ingestion can deteriorate rapidly. Whenever possible, the time of ingestion as well as the type, amount, and preparation (immediate- or sustained-release) of drug ingested should be determined. It is important to clarify whether the ingestion was accidental or intentional and to assess the patient for suicidality.

The hallmark of CCB overdose is circulatory shock due to bradycardia, poor cardiac contractility and profound peripheral vasodilation, which leads to tissue hypoperfusion and target organ damage.1 CCBs of all subclasses reduce pancreatic insulin secretion and induce end-organ insulin resistance causing hyperglycaemia. Metabolic side-effects include hyperglycaemia, hypoinsulinaemia and impairment of the cardiac myocyte adaptive response. Additionally, CCBs interfere with calcium-stimulated mitochondrial action and glucose catabolism which can result in lactate production and ATP hydrolysis contributing to acidosis.11 Significant bradycardia, hypotension, second- and third-degree heart block can occur especially with verapamil...
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Initial presentation with bradycardia and hypotension could be signs of toxicity from various pharmacological agents including beta blockers, tricyclic antidepressants, digoxin, clonidine, sedative-hypnotics, opioids and organophosphate poisoning. The presence of hyperglycaemia in a non-diabetic patient may help to distinguish CCB from beta blocker poisoning.6

Overdose management

Asymptomatic patients with normal vital signs require monitoring for at least 12 hours with standard-release preparations and for at least 24–36 hours if sustained/extended-release or once-a-day preparation was ingested.15,16 Activated charcoal (AC) as a single dose of 1 g/kg for children up to the adult dose of 50 g should be administered to patients within one hour of ingestion for standard-release preparations and within four hours of ingestion for SR preparations. AC should be administered even if the patient is asymptomatic but must be withheld in patients who cannot protect their airway and in patients with a depressed mental status. Orogastric lavage may be necessary in patients who present within one to two hours of a potentially dangerous ingestion for standard-release preparations and within four hours of ingestion for SR preparations. AC should be administered even if the patient is asymptomatic but must be withheld in patients who cannot protect their airway and in patients with a depressed mental status. Orogastric lavage may be necessary in patients who present within one to two hours of a potentially dangerous ingestion for standard-release preparations and within four hours of ingestion for SR preparations. AC should be administered even if the patient is asymptomatic but must be withheld in patients who cannot protect their airway and in patients with a depressed mental status. Orogastric lavage may be necessary in patients who present within one to two hours of a potentially dangerous ingestion for standard-release preparations and within four hours of ingestion for SR preparations. AC should be administered even if the patient is asymptomatic but must be withheld in patients who cannot protect their airway and in patients with a depressed mental status.

Other interventions in refractory cases as an adjuvant to vasopressors and HIET may include transvenous cardiac pacing, an intracoronary balloon pump and extracorporeal membrane oxygenation and cardiopulmonary bypass.29-31

Differential diagnosis

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**Table 1: Specific therapies in CCB overdose**

| CCB overdose                              | Treatment                                                                 |
|-------------------------------------------|---------------------------------------------------------------------------|
| Stabilise airway, breathing and circulation | Stabilisation of the airway as necessary (avoid induction agents that exacerbate hypotension). Fluid resuscitation 500 mL to 1 000 mL isotonic saline. (up to 20 mL/kg crystalloid). |
| Gastrointestinal decontamination          | Activated charcoal (1 g/kg up to 50 g maximum) in patients who are haemodynamically stable with normal mental status. Whole bowel preparation (2 L/hour by mouth until clear rectal effluent) for potentially life-threatening ingestion of extended-release preparation. |
| Bradycardia                                | Atropine IV 0.5–1.0 mg boluses, may repeat up to 3 total doses (0.02 mg/kg IV in paediatric patients). |
| Hypotension                                | Vasopressors IV: Adrenaline infusion 0.05–1 μg/kg/min. Note: Inotropic actions predominate at lower doses with vasoconstrictive actions at higher doses. Noradrenaline at 2 mcg/minute IV, titrated until systolic BP is 100 mmHg. |
| Hypotension and/or bradycardia             | Intravenous calcium salts: Calcium gluconate Bolus of 60 mL of 10% solution IV (0.6–1.0 mL/kg in children) OR calcium chloride 10 to 20 mL of 10% solution (0.2 mL/kg in children) via a central line. Repeat boluses can be given up to 3 times. Monitor serum level and ECG to exclude hypercalcaemia. High dose insulin therapy (HIET) and dextrose: Loading dose of 50% dextrose 1 mL/kg IV. Bolus of 1 unit/kg IV of regular insulin and be maintained at an infusion of 0.5 units/kg per hour. Maintained at 10% dextrose infusion to maintain normoglycaemia based on hourly glucose measurements. Glucagon IV administered at a dose of 1 to 5 mg IV and may be repeated twice. Nausea, vomiting, hyperglycaemia, hypokalaemia, and ileus can occur with bolus doses above 50 micrograms/kg. Lipid emulsion therapy (20% solution) administered at a bolus of 1.5 mL/kg over 2 minutes. The same dose may be repeated every three to five minutes if there is no response, for a total of three bolus doses. Infusion 1.5 mL/kg over 60 minutes. |
| Hyperglycaemia                             | Sodium bicarbonate: Adults: 8.4% sodium bicarbonate solution administered at a dose of 1 mEq/kg up to a maximum dose of 50 mEq, as an IV slow push and repeat doses should be guided by arterial blood gases. Infusions and children < 2 years of age: 4.2% (0.5 mEq/mL) solution should be used. |
| Severe metabolic acidosis                  | Potassium chloride infusion at rate 10 mmol/h. |

**Conclusion**

Severe CCB poisoning is life-threatening, and management is often challenging and requires immediate treatment. Clinicians should familiarise themselves with its management. Good outcomes can be achieved through aggressive treatment and provision of circulatory support. Psychiatric assessment in case of parasuicide is of paramount importance.

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