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Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies

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Management of cardiovascular instability resulting from calcium channel antagonist (CCB) or beta-adrenergic receptor antagonist (BB) poisoning follows similar principles. Significant myocardial depression, bradycardia and hypotension result in both cases. CCBs can also produce vasodilatory shock. Additionally, CCBs, such as verapamil and diltiazem, are commonly ingested in sustained-release formulations. This can also be the case for some BBs. Peak toxicity can be delayed by several hours. Provision of early gastrointestinal decontamination with activated charcoal and whole-bowel irrigation might mitigate this. Treatment of shock requires a multimodal approach to inotropic therapy that can be guided by echocardiographic or invasive haemodynamic assessment of myocardial function. High-dose insulin euglycaemia is commonly recommended as a first-line treatment in these poisonings, to improve myocardial contractility, and should be instituted early when myocardial dysfunction is suspected. Catecholamine infusions are complementary to this therapy for both inotropic and chronotropic support. Catecholamine vasopressors and vasopressin are used in the treatment of vasodilatory shock. Optimizing serum calcium concentration can confer some benefit to improving myocardial function and vascular tone after CCB poisoning. High-dose glucagon infusions have provided moderate chronotropic and inotropic benefits in BB poisoning. Phosphodiesterase inhibitors and levosimendan have positive inotropic effects but also produce peripheral vasodilation, which can limit blood pressure improvement. In cases of severe cardiogenic shock and/or cardiac arrest post-poisoning, extracorporeal cardiac assist devices have resulted in successful recovery. Other treatments used in refractory hypotension include intravenous lipid emulsion for lipophilic CCB and BB poisoning and methylene blue for refractory vasodilatory shock.

Introduction

Cardiovascular system (CVS) poisoning with calcium channel antagonists (CCBs) or beta-receptor antagonists (BBs) comprises a small percentage of all poisoning presentations [1]. Poisoning with these agents has the potential for significant systemic toxicity and high rates of mortality [2].

BBs competitively antagonize myocardial beta-1 adrenoceptors, which normally activate adenyl cyclase to increase cyclic AMP (cAMP) production and phosphorylation and opening of L-type calcium channels. Thus, BBs reduce the facilitation of calcium entry into cardiomyocytes produced by increased cAMP, resulting in negative chronotropic and inotropic effects. The resultant effect is a direct depressant action on the myocardium, resulting in conduction delays, bradycardia and reduced contractility with little or no effect on peripheral vasculature. Some agents, such as propranolol and labetalol, also antagonize voltage-gated sodium channels in overdose and might be associated with a higher risk of mortality than other BBs [3].

CCBs directly inhibit voltage-gated L-type calcium channel opening and calcium influx into myocardial and vascular smooth muscle cells. Calcium influx initiates excitation–contraction coupling, sino-atrial node depolarization in the myocardium and the maintenance of vascular and gastrointestinal (GI) smooth muscle tone. CCBs also inhibit L-type calcium channels in pancreatic Islet cells, reducing insulin secretion [4] and resulting in hyperglycaemia and reduced cardiac glucose utilization [4]. Hypotension from CCB poisoning can be multifactorial and result from a combination of negative myocardial inotropy and chronotropy as well as peripheral vasodilation.

Verapamil and diltiazem are the CCBs most commonly implicated in severe CVS toxicity following overdose. Both agents are commonly available in sustained-release (SR) formulations. Hence, the onset of toxicity can be delayed by several hours and the duration of toxicity can be prolonged owing to ongoing absorption from the GI tract. Negative inotropic and chronotropic effects are common and peripheral vasodilation can also contribute to hypotension [3].

The dihydropyridine CCBs (e.g. amlodipine, nifedipine) primarily affect vascular smooth muscle calcium channels and, in overdose, produce vasodilatory shock with reflex sinus tachycardia [3]. Direct cardiac toxicity, from loss of vascular smooth muscle calcium-channel specificity, has been observed in large overdoses and in children [5]. The clinical features of poisoning for both CCBs and BBs are summarized in Table 1.

Principles of management of shock in CCB and BB poisoning

Shock in BB and CCB poisoning will usually require management in the intensive care unit. Specialized toxicology advice, either from a poisons information centre or locally available toxicologist, might assist in the guidance of treatment.

It is important to determine whether the formulation of drug ingested is SR as the onset of toxicity can be delayed for several hours. Observation for 24 h in a monitored environment is required in all asymptomatic patients with SR formulation ingestions.

GI decontamination should be considered in all patients. With immediate-release (IR) drug ingestions, a single dose of activated charcoal can be administered within 4 h of ingestion. With SR preparations, whole-bowel irrigation (WBI) with a polyethylene glycol electrolyte mixture can be considered prior to the onset of symptoms. The onset of bradycardia and hypotension is associated with reduced GI function and ileus. As a result, WBI should not be instituted once the patient develops symptoms of toxicity.

The initial treatment of symptomatic BB and CCB poisoning is supportive. This includes early airway and respiratory support. Intravenous fluid administration, to treat hypotension, should be limited to 1–2 l to avoid fluid overload and pulmonary oedema, as patients are usually euvolaemic. Intravenous atropine can be administered in an attempt to reverse bradycardia but is rarely effective.

Shock in BB poisoning is the result of direct cardiac toxicity from bradycardia, conduction delays, negative inotropy and reduced cardiac output.

As a result, pharmacotherapy is aimed at improving myocardial contractility and bradycardia. Evidence of sodium channel antagonist effects (QRS widening on a 12-lead ECG, seizure activity) can occur in poisoning with some BB agents, such as propranolol and labetalol. Treatment might need to include serum alkalinization with intravenous hypertonic sodium bicarbonate, as used in cyclic antidepressant poisoning [6]. The clinical effects of toxicity are summarized in Table 1.

With CCBs, shock in verapamil and diltiazem poisoning can be the result of varying degrees of both cardiac toxicity and vasodilation. Treatment might require a combination of inotropic, chronotropic and vasoconstrictor agents. In dihydropyridine poisoning, the primary toxicity results from vasodilatory shock and vasopressors are indicated in the first instance.

If available, emergent bedside echocardiography or invasive cardiac output assessment (Pulse Contour Cardiac Output Measurement: (PiCCO) or pulmonary artery catheter) will assist in guiding inotrope and vasopressor selection.

Table 1

Summary of common clinical effects in calcium channel antagonist (CCB) and beta-adrenergic receptor antagonist (BB) toxicity

	Heart rate	Atrio-ventricular conduction	Myocardial contractility	Cardiac output	QRS interval	Systemic vascular resistance	Systemic effects
BB	↓				←→		
BB with membrane stabiliszing effect (propranolol/labetalol)	↓	↑PR-interval Slowed AV conduction 1st, 2nd, 3rd degree AV block	↓	↓	←→ or ↑	←→ or ↑	Sedation Coma Seizures Hypoglycaemia
Verapamil and diltiazem	↓	Asystole	↓	↓	←→	↑ or ↓	Hyperglycaemia
Dihydropyridine CCB	←→ or ↑	Uncommon Can occur in massive overdose	←→	←→ or ↑	←→	↓	Metabolic / lactic acidosis Seizures

←→ Unchanged; ↑ Increased; ↓ Decreased.

Specific therapies used in the treatment of shock from myocardial depression

The treatment of suspected cardiogenic shock in BB and CCB poisoning follows similar therapeutic principles. High-dose insulin euglycaemia therapy and catecholamine infusions form the mainstay of therapy to improve inotropy and chronotropy in both instances.

There are a number of second-line therapies that can be considered. In BB and CCB poisoning, phosphodiesterase inhibitors (PDEIs) can improve contractility. Glucagon can improve bradycardia in BB poisoning. In CCB poisoning, intravenous calcium infusion can have a benefit in increasing cardiac output and vascular tone. A stepwise approach to treatment is summarized in Table 2. Extracorporeal cardiac assist devices (ECADs) can be considered in cases refractory to pharmacotherapy.

High-dose insulin euglycaemic therapy (HIET) in BB and CCB poisoning

HIET has a number of mechanisms of action in cardiogenic shock in BB and CCB poisoning. Healthy myocardium utilizes free fatty acids as the primary energy

Table 2

Summary of common pharmacological agents used in the treatment of shock from calcium channel antagonist (CCB) and beta-adrenergic receptor antagonist (BB) poisoning

Indication	Treatment	Dosing	Desired clinical effect	Adverse events
Suspected or documented cardiogenic shock in BB or CCB intoxication	High-dose insulin euglycaemia	Loading dose 1 IU kg^{-1}	Positive inotrope	Hypoglycaemia
		Infusion 1–10 IU kg^{-1} h^{-1}	Increased cardiac output	Hypokalaemia
		With	Increased BP	Mild vasodilation
		50% glucose infusion to maintain euglycaemia	Reduced catecholamine infusion requirements	No effect on heart rate
	Inotropic/chronotropic catecholamines:	Titrated infusion to effect	Adrenaline:	Adrenaline:
			Positive inotrope and chronotrope	Possible increase in BP from alpha-adrenergic vasoconstriction with no increase or fall in cardiac output
	adrenaline	0.05–1 μg kg^{-1} min^{-1}	Increased contractility and heart rate	Hyperglycaemia
				Lactic acidaemia
			→ increased cardiac output and BP	Limb ischaemia
	Isoprenaline	0.5–5 μg min^{-1} (up to 20 μg min^{-1})	Isoprenaline:	Isoprenaline:
			Positive inotrope and chronotrope	Ventricular arrhythmias
			Increased heart rate, contractility	Worsening of hypotension from beta-2 adrenoceptor stimulation
			→ increased cardiac output and BP	
	Phosphodiesterase inhibitors (e.g. milrinone, enoximone)	Varies depending upon agent selected	Increased cardiac output	Vasodilation worsening hypotension
				Ventricular arrhythmias
CCB toxicity with suspected hypotension from cardiogenic shock and/or vasodilatory shock	Calcium infusion	Loading dose: 0.6 ml kg^{-1} of 10% calcium gluconate) Infusion: 0.6–1.6 ml kg^{-1} h^{-1}	Increased BP from improved cardiac output and/or SVR	Effect can be transient
		Aim for serum ionized calcium up to 2 × reference range		No effect on heart rate
Suspected or documented vasodilatory shock from CCB poisoning	Alpha-adrenergic agonists (noradrenaline, phenylephrine, metaraminol)	Titrated infusion dosing to effect	Improvement in BP	Possible increase in BP from alpha-adrenergic vasoconstriction with no increase in cardiac output
			Increased SVR	
				Hyperglycaemia
				Lactic acidaemia
	Vasopressin	Titrated dosing up to maximum of 0.04 IU min^{-1}	Improvement in BP	Limb ischaemia
			Increased SVR	

BP, blood pressure; SVR, systemic vascular resistance.

source. In shock states, glucose is the preferred energy substrate. HIET increases the intracellular transport of glucose, lactate and oxygen into myocardial cells [7]. Insulin also has calcium-dependent inotropic effects mediated by phosphatidylinositol 3-kinase (PI3K) [8]. Insulin produces terminal arteriole vasodilation of coronary, pulmonary and systemic vasculature by enhancing endothelial nitric oxide synthase activity, which results in the homogenization of blood flow at the microcirculatory level [9].

In animal models of verapamil and propranolol poisoning, HIET provided greater haemodynamic stability and survival compared to adrenaline or glucagon alone [2, 7, 10]. In clinical cases, significant improvements in blood pressure (BP) and haemodynamic stability have been reported following poisoning in mono- and multidrug intoxications of verapamil, diltiazem, amlodipine, propranolol and other BBs [4, 11–16]. The onset of effect for HIET has been reported to occur between 15 min and 60 min after initiating therapy [4, 11, 12, 14]. Cardiac output and BP improve, with little effect on heart rate. HIET can allow weaning of, and reduce the negative metabolic effects often seen with, high-dose catecholamine infusions. It is unlikely to improve vasodilatory shock as seen with dihydropyridine CCB intoxication [3, 17].

Complications of HIET include hypoglycaemia [3, 14, 18] and hypokalaemia [3, 12] from the intracellular potassium shift.

In suspected or documented cardiogenic shock from CCB or BB poisoning, HIET should be commenced early. A loading dose of 0.5–1 IU kg^{-1}, with infusion titrated at 0.5–2 IU kg^{-1} h^{-1} is a starting point [8, 12]. Haemodynamic benefit has been reported with doses up to 10 IU kg^{-1} h^{-1} in a porcine model of propranolol poisoning [19] and similar infusion rates have been used in severe clinical cases of CCB and BB poisoning with apparent effect [20]. When preparing an insulin infusion, it is important to ensure that the concentration of the infusion is at least 10 IU ml^{-1}. This is especially important when infusing higher doses, to prevent fluid overload.

HIET is supplemented with intravenous glucose (10–50%) to maintain euglycaemia. The higher concentration will limit excess free water administration. The glucose requirement does not significantly increase with increasing insulin dose [20].

Serum potassium concentration should be monitored regularly. The aim of potassium supplementation is to maintain the serum concentration at more than 3 mmol l^{-1}. Importantly, the serum potassium falls as a result of the intracellular shift during insulin therapy rather than body loss of this ion. Hence, total body potassium stores can be normal.

A lack of haemodynamic response suggests that other therapies should be considered or that shock is vasodilatory in aetiology.

Catecholamine adrenergic receptor agonists in BB and CCB poisoning

Clinicians are familiar with the use of catecholamines in the treatment of shock. In BB and CCB poisoning, the response to catecholamines can be unpredictable and very high doses can be required to achieve a response. In BB poisoning, a lack of response can be related to the degree of competitive beta-1 adrenoceptor antagonism. No single catecholamine has been shown to be superior to others in BB and CCB poisoning. As a result, the choice of catecholamine needs to be based upon the haemodynamics of the particular patient, balancing low cardiac output against low systemic vascular resistance (SVR). Importantly, the goal of therapy is improved tissue perfusion and not just a favourable BP reading.

Adrenaline infusion has positive inotropic and chronotropic effects on the myocardium in both BB and CCB poisoning. However, in severe poisoning, escalating doses can result in an increase in BP through its vasoconstrictive effects on peripheral alpha-1 adrenoceptors, without an improvement in cardiac output or tissue perfusion [21]. Metabolic effects such as hyperglycaemia, lipolysis, tissue insulin resistance and lactic acidaemia from peripheral vasoconstriction and tissue ischaemia can result in further clinical deterioration [7].

Isoprenaline is a beta-1 and -2 adrenoceptor agonist that is also used for its chronotropic and inotropic effects in BB poisoning. It can worsen hypotension by beta-2 adrenoceptor stimulation and vasodilation of the muscle bed vasculature. If necessary, the addition of a vasopressor might circumvent this effect [22]. Dobutamine and dopamine use has also been reported in the treatment of cardiogenic shock from BB and CCB poisoning; the associated risks include paradoxical hypotension, as with isoprenaline [22].

There are no trials directly comparing the effectiveness of catecholamines alone to HIET in humans with BB or CCB poisoning. However, the use of high-dose catecholamine infusions has resulted in favourable outcomes without the addition of HIET, although significant lactic acidaemia and hyperglycaemia can result [23].

PDEIs for cardiogenic shock in BB and CCB poisoning

PDEIs, such as milrinone, amrinone, and enoximone, increase myocardial inotropy by increasing intracellular cAMP activity independently of adrenergic receptors. However, the cAMP concentration also increases in vascular smooth muscle, resulting in vasodilation, which can exacerbate hypotension [24]. Haemodynamic parameters have improved with amrinone infusion in both labetalol and verapamil poisoning that is unresponsive

to catecholamines and glucagon [25, 26]. In a case of cardiac arrest following propranolol poisoning, enoximone infusion resulted in the return of circulation and survival [27]. Due to the limited experience with PDEIs in poisoning, they should be considered as third-line options when other vasoactive agents have failed. Optimal dosing regimens are unclear.

Calcium supplementation in CCB poisoning

Calcium supplementation can be considered in CCB poisoning, in concert with HIET and catecholamine infusions. However, the effect of calcium infusion is not consistent. Alone, it is unlikely to provide a sustained benefit on haemodynamics in CCB poisoning. Observational studies have shown no clear dose–response relationship with calcium administration between responders and nonresponders [28].

Calcium can be used as a temporizing measure while preparing other inotropic agents. A suggested dosing regimen includes utilizing a loading dose (0.6 ml kg^{-1} of 10% calcium gluconate) and infusion (0.6–1.6 ml kg^{-1} h^{-1}) titrated to haemodynamic parameters and a serum ionized calcium up to two times the upper limit of the reference range [11]. It is unlikely that calcium alone will provide adequate ongoing support of haemodynamics in severe poisoning. Calcium infusion is not routinely recommended in BB toxicity.

Other treatments for bradycardia and heart block in BB and CCB toxicity

Atropine is currently recommended as a standard advanced cardiac life-support measure for symptomatic bradycardia. Although this can be administered following poisoning with these agents, it is unlikely to have a significant or persisting effect on heart rate. Care should be taken not to exceed the recommended maximum dose (3 mg), as this is can result in the development of anticholinergic toxidrome and delirium.

High-dose glucagon in BB poisoning

High-dose glucagon produces positive inotropic and chronotropic actions on heart muscle. These are mediated through a glucagon receptor that increases cAMP production independently of beta-adrenoceptors. In animal models of CCB and BB poisoning, glucagon exerts its effect primarily as a positive chronotrope, with little or no effect on BP [29]. A number of positive case reports have been reported in BB and CCB poisoning [11, 29, 30]. However, glucagon has rarely been a sole agent reported in the treatment of intoxication with these agents. The onset of clinical effect is expected within a few minutes of a single dose and persists for 10–15 min [31]. Owing to its short half-life, an infusion is required to maintain an effect. Adverse effects include nausea, vomiting and hyperglycaemia.

The recommended loading dose in poisoning is 5–10 mg in an adult, followed by an infusion from 1 mg h^{-1} to 10 mg h^{-1}. Glucagon can be considered a second-line treatment in BB poisoning. However, it might not be available in sufficient quantities to maintain a continuous infusion. Dosing with other inotropic agents, such as HIET and catecholamine infusions, should be optimized first.

Cutaneous and transvenous pacing have been utilized in both CCB and BB poisoning with symptomatic bradycardia. Ventricular capture with pacing is unpredictable. In addition, heart rate can increase without an improvement in BP. However, pacing can be considered in the multimodal approach, along with other pharmacological treatments in cases of severe poisoning.

Specific therapies used in the treatment of vasodilatory shock from CCB poisoning

Alpha-adrenoceptor agonists

Alpha-adrenoceptor agonists, such as noradrenaline, phenylephrine and metaraminol, improve vascular tone in cases of vasodilatory shock from CCB poisoning. These are usually considered as first-line therapy in dihydropyridine CCB poisoning and might also be required in cases of suspected or documented vasodilatory shock in verapamil or diltiazem poisoning (Table 2).

Vasopressin

Vasopressin is synthesized in the hypothalamus. Vasoconstriction results from activation of V1 vascular receptors, modulation of ATP-activated potassium channels, modulation of nitric oxide and potentiation of adrenergic vasoconstrictors [24, 32]. In studies of vasodilatory shock from sepsis and cardiopulmonary bypass, the addition of vasopressin to noradrenaline improved BP [32]. In two patients poisoned with amlodipine and diltiazem, respectively, improvement in SVR and BP was seen following the addition of vasopressin, to HIET, vasopressors and calcium [33]. Other case reports have described the use of vasopressin as part of the management of severe CCB poisoning but did not attribute specific benefit to its use [34].

Vasopressin has not shown any benefit in animal models of BB intoxication [35, 36]. There are currently no reports of its successful use in clinical BB toxicity.

The adverse effects of vasopressin include reduced cardiac output, limb ischaemia and an association with cardiac arrest at higher doses. Doses should not exceed 0.04 IU min^{-1} [24, 32].

Vasopressin can be added to therapy in vasodilatory shock that is unresponsive to catecholamine vasopressors in CCB poisoning or in poisoning where CCBs are co-ingested with other vasodilators (Table 2).

Other therapies reported in the treatment of refractory shock in BB and CCB poisoning

Other therapies reported in the treatment of refractory shock in BB and CCB poisoning are summarized in Table 3.

Levosimendan

Levosimendan is an inotropic agent that sensitizes myocardial troponin-C to calcium, thus increasing cardiac myocyte responsiveness to calcium and increasing myocardial contractility. It is also a vasodilator [24, 37]. Levosimendan increases cardiac output in animal models of CCB and BB toxicity but does not increase BP. There is minimal clinical experience to guide the use of this agent in either BB or CCB intoxication (Table 3).

ECADs

If hypotension persists or cardiac arrest ensues in spite of the use of HIET, catecholamine inotropes, vasopressors and intravenous lipid emulsion (ILE), mechanical modalities, such as cardiac bypass and ECADs, have been used successfully to support patients until cardiac function returns. Given the reversible nature of many poisonings, ECADs can allow time for drug redistribution and/or metabolism to a point where cardiac function in an otherwise healthy heart is restored [38, 39]. ECADs are not

Table 3

Summary of treatments to consider in cases where shock or bradycardia is unresponsive to standard therapies

Treatment	Indication	Dosing	Desired effect	Potential adverse reactions
Glucagon	BB toxicity	Loading-dose:	Primarily positive chronotropic action	Nausea, vomiting
	Bradycardia and cardiogenic shock	5–10 mg	Increased heart rate →	Hyperglycaemia
		Infusion: 2–5 mg h^{-1}	Increased BP	Not enough glucagon available to sustain infusion
Levosimendan	Cardiogenic shock	Variable	Increased cardiac output	Vasodilation worsening hypotension
				Ventricular arrhythmias
Cardiac transvenous/cutaneous pacing	Symptomatic bradycardia and heart block in BB and CCB poisoning	Not applicable	Increased heart rate	Failure to capture heart rate
				Heart rate may increase without change in BP
				Ventricular arrhythmia
				Ventricular perforation
Extracorporeal cardiac assist devices	Cardiogenic shock	Not applicable	Mechanical support of cardiac output	Local:
			Not effective in vasodilatory shock	Limb ischaemia, DVT
				Systemic:
				Coagulopathy, bleeding, haemolysis, septicaemia, systemic thromboembolism
Intravenous lipid emulsion	Refractory cardiogenic or vasodilatory shock	Loading dose: 1.5 ml kg^{-1} 20% lipid emulsion	Improvement in BP, perfusion, heart rate	Lipaemic plasma. Inability to analyse blood biochemistry
				Blood hyperviscosity
		Infusion: 0.25 ml kg^{-1} min^{-1} to a total volume of 10 ml kg^{-1}		Pancreatitis
				Noncardiogenic pulmonary oedema
Methylene blue	Refractory vasodilatory shock	Loading dose 1–2 mg kg^{-1}	Improvement in hypotension	Blue discolouration of the skin, secretions
			Reduction in vasopressor dosing	Haemolysis
				Methaemoglobinaemia
				Serotonin syndrome in presence of serotonergic agonists, MAOIs, SSRIs

BB, beta-adrenergic receptor antagonist; BP, blood pressure; CCB, calcium channel antagonist; DVT, deep-vein thrombosis; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

effective in cases of refractory vasodilatory shock where cardiac output is already increased (Table 3).

ILE

ILE has been recommended as a rescue therapy in cases of severe toxicity resulting from poisoning with a wide range of lipophilic local anaesthetic, pharmaceutical and chemical agents [40] (see Table 3).

The response to ILE in clinical intoxication with BBs and CCBs is variable. In most cases, ILE was administered as a 'rescue therapy' in verapamil or diltiazem poisoning, or as a part of poly-drug intoxications that included BBs with CCBs. A positive response has been reported within an hour of ILE administration in some cases [15, 41, 42], or several hours after institution of therapy in others [43, 44]. A lack of effect on haemodynamics has also been reported [45].

In BB poisoning, ILE has been administered with apparent effect in cases of hypotension or asystole unresponsive to other inotropes in propranolol, bisoprolol, carvedilol, nebivolol and atenolol poisoning [46]. Adverse events observed after ILE administration for CVS toxicity include lipaemic serum interfering with biochemical assays, pancreatitis and acute lung injury [47].

ILE can be considered in lipophilic CCB or BB intoxication in which hypotension is unresponsive to other therapies. A suggested dosing regimen includes a loading dose of 1.5 ml kg^{-1} of 20% lipid emulsion followed by 0.25 ml kg^{-1} min^{-1} for 30–60 min, to a maximum of 10 ml kg^{-1} as a total dose [48]. It is unclear whether ILE infusion enhances the absorption of lipophilic toxins from the GI tract and paradoxically increases toxicity [49].

Methylene blue (MB) for refractory vasodilatory shock in CCB poisoning

MB has been used in the treatment of vasodilatory shock post-cardiac surgery, and in septicaemia, anaphylaxis and drug-induced shock. It inhibits the nitric oxide–cyclic guanosine monophosphate pathway, scavenges nitric oxide (NO) and inhibits NO synthesis [50]. This might be of relevance to poisoning from CCBs, such as amlodipine, which enhance the release of NO [50].

An MB-induced clinical improvement in hypotension from vasodilatory shock has been described in poisoning cases unresponsive to vasopressors, in amlodipine [51, 52] and quetiapine [53] overdose. BP improved within 1 h of MB infusion, and vasopressors were rapidly weaned. The recommended dose of MB is 1–2 mg kg^{-1} as a single injection [50]. Adverse effects include vomiting, dyspnoea and haemolytic anaemia may occur at higher doses. MB is also a reversible inhibitor of monoamine oxidase A, and can cause serotonin toxicity in the presence of co-ingested serotonergic agents [54].

Conclusion

The treatment of severe CCB and BB poisoning can be challenging. A multimodal therapeutic approach is often required (Table 2).

BB poisoning most commonly results in shock from myocardial depression; bradycardia and reduced contractility. Treatment is aimed at increasing heart rate and myocardial contractility. The first-line therapies are HIET and inotropic catecholamine infusion (adrenaline or isoprenaline).

Shock in CCB poisoning can be the result of myocardial depression and/or peripheral vasodilation. In general, verapamil and diltiazem are more likely to produce cardiogenic shock that should be treated with HIET and adrenaline infusions in the first instance. However, vasodilatory shock can play a part in their toxicity, and the addition of vasopressors might be necessary. Echocardiography or invasive haemodynamic monitoring can assist in the assessment of the type of shock predominating in these cases. Dihydropyridine poisoning is more likely to present with vasodilatory shock and reflex tachycardia. Vasopressors are indicated in the first instance. Intravenous calcium administration can have a moderate effect on hypotension in all CCB poisoning, although it is unpredictable.

In cases where the above-mentioned therapies do not result in haemodynamic improvement, other strategies, such as cardiac pacing, PDEIs and high-dose glucagon infusion can be considered on a case-to-case basis. However, the benefits of these can vary, depending upon the toxicant. In refractory toxic cardiogenic shock and cardiac arrest, ECADs have resulted in successful outcomes. Finally, in cases of cardiac arrest or ongoing severe hypotension, prolonged cardiopulmonary resuscitation should be considered, in concert with toxicological consultation to ensure that all treatment options have been considered prior to any consideration of treatment cessation.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work.

Contributors

AG reviewed and edited all sections of the review article written by co-authors; and was responsible for primary of the literature for the sections on glucagon, lipid emulsion, extracorporeal assist devices and catecholamine, as well as the introduction and conclusion;

and was the primary editor for all revisions and responses to reviewers. HML carried out the primary review of the literature for calcium and high-dose insulin. DD carried out the primary review of the literature for vasopressin, methylene blue, phosphodiesterase inhibitors and levosimendan.

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