

REVIEW ARTICLE

Treatment for calcium channel blocker poisoning: A systematic review

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Context. Calcium channel blocker poisoning is a common and sometimes life-threatening ingestion. **Objective.** To evaluate the reported effects of treatments for calcium channel blocker poisoning. The primary outcomes of interest were mortality and hemodynamic parameters. The secondary outcomes included length of stay in hospital, length of stay in intensive care unit, duration of vasopressor use, functional outcomes, and serum calcium channel blocker concentrations. **Methods.** Medline/Ovid, PubMed, EMBASE, Cochrane Library, TOXLINE, International pharmaceutical abstracts, Google Scholar, and the gray literature up to December 31, 2013 were searched without time restriction to identify all types of studies that examined effects of various treatments for calcium channel blocker poisoning for the outcomes of interest. The search strategy included the following Keywords: [calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent OR (amlodipine or bencyclane or bepridil or cinnarizine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or prenylamine or verapamil or diltiazem)] AND [overdose OR medication errors OR poisoning OR intoxication OR toxicity OR adverse effect]. Two reviewers independently selected studies and a group of reviewers abstracted all relevant data using a pilot-tested form. A second group analyzed the risk of bias and overall quality using the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) checklist and the Thomas tool for observational studies, the Institute of Health Economics tool for Quality of Case Series, the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, and the modified NRCNA (National Research Council for the National Academies) list for animal studies. Qualitative synthesis was used to summarize the evidence. Of 15,577 citations identified in the initial search, 216 were selected for analysis, including 117 case reports. The kappa on the quality analysis tools was greater than 0.80 for all study types. **Results.** The only observational study in humans examined high-dose insulin and extracorporeal life support. The risk of bias across studies was high for all interventions and moderate to high for extracorporeal life support. **High-dose insulin.** High-dose insulin (bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) was associated with improved hemodynamic parameters

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and lower mortality, at the risks of hypoglycemia and hypokalemia (low quality of evidence). *Extracorporeal life support.* Extracorporeal life support was associated with improved survival in patients with severe shock or cardiac arrest at the cost of limb ischemia, thrombosis, and bleeding (low quality of evidence). *Calcium, dopamine, and norepinephrine.* These agents improved hemodynamic parameters and survival without documented severe side effects (very low quality of evidence). *4-Aminopyridine.* Use of 4-aminopyridine was associated with improved hemodynamic parameters and survival in animal studies, at the risk of seizures. *Lipid emulsion therapy.* Lipid emulsion was associated with improved hemodynamic parameters and survival in animal models of intravenous verapamil poisoning, but not in models of oral verapamil poisoning. *Other studies.* Studies on decontamination, atropine, glucagon, pacemakers, levosimendan, and plasma exchange reported variable results, and the methodologies used limit their interpretation. No trial was documented in humans poisoned with calcium channel blockers for Bay K8644, CGP 28932, digoxin, cyclodextrin, liposomes, bicarbonate, carnitine, fructose 1,6-diphosphate, PK 11195, or triiodothyronine. Case reports were only found for charcoal hemoperfusion, dialysis, intra-aortic balloon pump, Impella device and methylene blue. *Conclusions.* The treatment for calcium channel blocker poisoning is supported by low-quality evidence drawn from a heterogeneous and heavily biased literature. High-dose insulin and extracorporeal life support were the interventions supported by the strongest evidence, although the evidence is of low quality.

Keywords Antidotes; Calcium channel blockers; Cardiotoxins; Drug overdose; Poisoning; Toxicity; Treatment

Introduction

American Poison Control Centers report cardiovascular drugs as the substance category with the third fastest rate of increase in terms of exposures.¹ According to the National Poison Data System, calcium channel blockers (CCB) were responsible for at least 11,764 exposures and 78 deaths in 2011 in the United States.¹ This underestimates the real burden of such poisoning. A Canadian study of CCB poisonings² found that a poison control center was consulted in only 74% of cases. In order to help clinicians to best treat CCB poisoning, the development of practice guidelines on the treatment of CCB poisoning is warranted.

Therefore, the goal of this systematic review was to document and characterize the available evidence to facilitate development of guidelines following the GRADE (Grading of Recommendations Assessment, Development and Evaluation methodology)³ and the AGREE (Appraisal of Guidelines Research & Evaluation) II statement.⁴

Objective

The objective of this systematic review (registry number: CRD42012002823) was to evaluate the reported effects of treatments for CCB toxicity. The primary outcomes of interest were mortality and improvement in hemodynamics. The impact of interventions on secondary outcomes, such as functional outcomes, length of stay (LOS) in hospital, LOS in intensive care unit (ICU), duration of vasopressor use, and serum CCB concentrations, was also evaluated.

Methods

Eligibility criteria

Study types

Controlled trials, observational studies, case series, animal studies, case reports, and abstracts from scientific and clinical meetings in any language, without date restriction, were included. Case reports were defined as articles pertaining to a single case, whereas articles were classified as case series when multiple cases were presented. Cohort studies were differentiated from case series based on an approach proposed by Dekkers et al.⁵

Participants

Studies were eligible if they involved humans or animals poisoned with any CCB. Poisoning was defined as an “*exposure (...) causing or capable of causing toxicity, regardless of intent.*”⁶ An adverse effect was defined as an undesirable effect of a drug taken at therapeutic doses for the appropriate indication.

Interventions

Studies with defined intervention(s) meant to improve the targeted primary and/or secondary outcomes were eligible.

Outcome measures

Studies were required to document at least one of the primary or secondary outcomes. The primary outcomes included mortality (in hospital, or at the end of experiment for animal studies) and improvement in hemodynamic parameters (heart rate, blood pressure, stroke volume, cardiac output, and peripheral vascular resistance). The secondary outcomes included functional outcomes (defined as return to functional baseline or not), LOS in ICU, LOS in hospital, duration of vasopressor use, and serum CCB concentrations. Reported adverse effects of treatments were also documented.

Search strategy

Medline/Ovid, PubMed, EMBASE, Cochrane Library, TOXLINE, and International pharmaceutical abstracts up to December 31, 2013 were searched without time restrictions. Two librarians developed the search strategy using the following Keywords: [calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent OR (amlodipine or bencyclane or bepridil or cinnarizine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or mibefradil or nifedipine or nifedipine or nimodipine or nisoldipine or nitrendipine or prenylamine or verapamil or diltiazem)] AND [overdose OR medication errors OR poisoning OR intoxication OR toxicity OR adverse effect]. Conference proceedings and meeting abstracts of the EAPCCT (European Association of Poisons Centres and Clinical Toxicologists) and NACCT (North American Congress of Clinical Toxicology) (2008–2013), trial registries, and Google Scholar were also searched. Authors of selected publications were contacted.

Two independent reviewers blinded to authors and journal names selected the studies based on eligibility criteria. Disagreements were resolved by consensus or, when required, by a third reviewer. The kappa statistic was used to quantify agreement on the articles included. A data abstraction form to standardize the data collection process was used after a pilot version was tested among data abstractors with five articles related to digoxin poisoning. No significant abstraction difference was noted between abstractors. For each included study, two reviewers independently abstracted study characteristics (year of publication, authors, and study design), subjects (number, inclusion/exclusion criteria, age, gender, co-morbidities, co-ingestions, type of animal studied where applicable, sample size calculation, and weight for animal studies), treatment and control group characteristics, CCB involved (type, dose, route, and form), treatment(s) provided, outcomes, and results. To ensure uniformity, an independent individual merged the data collection into a single flow sheet.

Two independent reviewers carried out quality analysis for all of the studies except case reports. Disagreements were resolved by consensus or by a third party if required. The Cochrane risk of bias tool⁷ was not required because no controlled trials were found. The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) checklist⁸ and the Thomas tool⁹ were used for observational studies, the Institute of Health Economics tool¹⁰ for case series, and the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines¹¹ and the modified NRCNA (National Research Council for the National Academies) checklist¹² for animal studies. The percent agreement was documented for each item, and the kappa statistic was calculated for each type of quality analysis tool. Qualitative synthesis was used to summarize the evidence for each outcome. A planned meta-analysis was not performed due to heterogeneity of studies, interventions, and outcomes. The search strategy identified 15,577 citations. Two reviewers selected 216 articles (Kappa on articles inclusion = 0.85, 95% CI: 0.73–0.89) (Supplementary Appendix 1, to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827>). Six full-text articles were not found because the foreign language journals were inaccessible.^{13–18} Professional translation was performed on 23 manuscripts. A list of the articles translated and excluded after full-text review is available upon request.

Results

No controlled trial fulfilling eligibility criteria was identified. Human observational studies were published only for high-dose insulin^{19–21} and extracorporeal life support.²² Comparative studies included observational studies^{20,21} evaluating two different high-dose insulin regimens and one comparing high-dose insulin to vasopressors.¹⁹ One human observational study compared extracorporeal life support with standard therapy.²²

Results of individual studies and risks of bias for medical interventions

Table 1 describes results of included articles^{2,19–234} for the interventions for which there is the highest level of evidence. A more detailed description is available online (Supplementary Appendix 2 to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827>). Published case reports for each intervention is also available online (Supplementary Appendix 3 to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827>).

Gastrointestinal decontamination

Five human case series,^{23–27} including two pediatric studies,^{23, 24} reported sequelae-free survival of all patients who underwent gastrointestinal decontamination (including activated charcoal, gastric lavage, and whole-bowel irrigation). Cardiac arrests following initiation of whole-bowel irrigation were documented in two case series of hemodynamically unstable patients,^{28,29} and following gastric lavage in one case report.³⁰ In all cases, complications occurred after the patient began vomiting. Given the nature of these reports, neither survival nor cardiac arrest can be attributed, with confidence, to the decontamination procedures.

High-dose insulin

High-dose insulin (intravenous (IV) bolus of 1.0 unit/kg followed by a 0.5–2.0 unit/kg/h infusion) showed an improvement in hemodynamics in one of two human observational studies,^{20,21} all five human case series,^{31–35} and all four animal studies^{36–39} assessing that outcome, while a survival benefit was reported in animal studies.^{36,39} Hypoglycemia (1 of 7²¹ and 2 of 4³² subjects) and hypokalemia (2 of 7²¹ and 2 of 4³² subjects) were reported as adverse effects in human cohort studies and case series, respectively.

Calcium

The majority of animal studies^{40–46} evaluating use of calcium demonstrated a reduced mortality as well as hemodynamic improvement. Human case series^{47–57} and case reports^{58–78} demonstrated inconsistent benefits, but adverse effects such as hypercalcemia were rare. The dose employed was typically an IV single dose of calcium chloride (1–5 g), sometimes followed by an infusion, or the equivalent dose in calcium gluconate.

Vasopressors

An unblinded study³⁶ using a porcine model of nifedipine-induced cardiogenic shock showed no differences in mortality or hemodynamic parameters (cardiac output, blood pressure, and systemic vascular resistance), following addition of phenylephrine to high-dose insulin (10 units/kg/h). Vasopressin was reported as potentially harmful in one blinded randomized controlled trial using a swine model of verapamil poisoning,⁷⁹ although one case series of two patients⁸⁰ and one case report⁸¹ showed blood pressure improvement when added to other vasopressors. Epinephrine was associated with increased cardiac output in animal studies,^{39,43,45} but hyperglycemia and

Table 1. Results of individual studies and risks of bias.

Source	Intervention	Participants	Outcomes	Methodological quality
<i>Observational studies</i>				
Musselman et al. (2011) ¹⁹	HDI ± glucagon vs vasopressors only	20 with beta-blocker or CCB poisonings requiring vasopressors (10 in the intervention group)	STROBE and Thomas tool – Hemodynamics: no significant difference in MAP (no power calculation) – LOS in hospital or ICU: no significant difference (no power calculation)	STROBE: 6/22 Thomas tool: • Moderate: Selection bias • Weak: Cohort methods, confounders, blinding, data collection, withdrawals, analysis, intervention integrity
Bryant et al. (2009) ²⁰	HDI: 0.5–1.0 units/kg bolus followed by 0.5–1.0 units/kg/h infusion started preceding or shortly after vasopressors vs other form of providing HDI	46 poisoned with a hemodynamically unstable CCB treated with HDI (19 in the intervention group)	– Mortality: higher when the HDI is not provided as per the protocol	STROBE: 4/22 Thomas tool: • Weak: Selection bias, case-control methods, confounders, blinding; weak, data collection, withdrawals, analysis, intervention integrity
Greene et al. (2007) ²¹	HDI: 0.5–2.0 units/kg/h with vs without 1 unit/kg bolus	7 poisoned with a hemodynamically unstable CCB treated with HDI (3 in the intervention group)	– Mortality: 1/7 (did not receive a bolus) – Hemodynamics: increase in more than 10 mmHg Systolic blood pressure (SBP) only in the group receiving a bolus – Mean LOS in ICU: 2.7 days – Adverse effects: 1 non-clinically significant hypoglycemia (no bolus) and 2 non-clinically significant hypokalemia (1 with bolus, 1 without)	STROBE: 9/22 Thomas tool: • Moderate: Selection bias, confounders, blinding, withdrawals • Weak: Cohort methods, data collection, analysis, intervention integrity
<i>Case series</i>				
Espinoza et al. (2013) ³¹	HDI: 0.5–1 units/kg bolus followed by 0.5–1 units/kg/h	46 poisoned with CCB	Institute of Health Economics tool for quality of case series and quality of reporting – Mortality: 9/46 – Adverse effects: no hypoglycemia	10/20 (2 unclear)
Holger et al. (2011) ³²	HDI bolus with dextrose followed by 1 unit/kg/h, increasing Q15 min by 1–2 units/kg/h up to 10 units/kg/h	4 poisoned with amlodipine, verapamil, or diltiazem	– Mortality: 0/4 – Hemodynamics: vasopressors could be tapered off with HDI – LOS in ICU, 2, 3, 5, and 30 days – Adverse effects: 2/4 hypoglycemia, 2/4 hypokalemia	13/20 (4 unclear)
Boyer et al. (2002) ³³	HDI: 0.5–1 units/kg/h	3 poisoned with diltiazem, amlodipine, or verapamil	– Mortality: 0/3 – Hemodynamics: improvement in blood pressure within 30 min – Adverse effects: hypoglycemia, hypokalemia	5/20 (5 unclear)
Boyer et al. (2001) ³⁴	HDI: 0.5 units/kg/h	2 poisoned with amlodipine or diltiazem	– Adverse effects: hypoglycemia, hypokalemia	4/20 (4 unclear)
Yuan et al. (1999) ³⁵	HDI: 4–70 units/h	4 poisoned with verapamil SR or amlodipine	– Hemodynamics: rapid reversal of hemodynamic collapse in both patients – Mortality: 0/3 (1 not reported) – Hemodynamics: improvement in blood pressure in all cases – LOS in hospital, 5–14 days – adverse effects: hypoglycemia	4/20 (8 unclear)
Case reports (see Supplementary Appendix to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827):				
– Improvement in hemodynamics reported in 18 cases ^{60,63,157–167,171,173,174,176,178,179}				
– No improvement in hemodynamics reported in 3 cases ^{76,168,172}				
– Adverse effects: Volume overload in 1 case ¹⁶⁷ and hypoglycemia reported in 1 case ¹⁷⁵				

(Continued)

Table 1. (Continued)

Animal studies		ARRIVE guidelines and Modified NRCNA	
Engebretsen et al. (2010) ³⁶	<p>Group 1: NS</p> <p>Group 2: HDI, 2 units/kg/h, increased Q10 min by 2 units/kg/h and max 10 units/kg/h</p> <p>Group 3: HDI and phenylephrine</p>	<p>15 Yorkshire pigs poisoned with nifedipine of 0.0125 mg/kg/min until 25% of baseline Mean arterial pressure (MAP) X Cardiac output (CO)</p> <p>– Mortality: 4/5 deaths in group 1 compared to 1/5 in group 2 and no death in group 3</p> <p>– Hemodynamics: groups 2–3 had significant improvement in MAP compared to group 1, but no significant difference in hemodynamics between groups 2 and 3</p> <p>– Adverse effects: hypoglycemia and hypokalemia</p>	<p>ARRIVE: 18/20</p> <p>NRCNA: 8/16</p>
Kline et al. (1997) ³⁷	<p>Group 1: NS</p> <p>Group 2: epinephrine</p> <p>Group 3: glucagon</p> <p>Group 4: HDI, 1000 nU/min, with dextrose</p>	<p>20 Mongrel dogs randomized to 4 groups, poisoned with intraportal verapamil infusion of 0.04 mg/kg/min × 1 h then 0.08 mg/kg/min × 1 h then 0.1 mg/kg/min × 1 h then 0.2 mg/kg/min until death</p> <p>– Hemodynamics: significant improvement in heart rate and blood pressure compared to all other groups</p>	<p>ARRIVE: 17/20</p> <p>NRCNA: 9/16</p>
Kline et al. (1996) ³⁸	<p>Group 1: NS</p> <p>Group 2: HDI</p> <p>Group 3: HDI without verapamil toxicity</p>	<p>18 Mongrel dogs randomized to 3 groups poisoned with intraportal verapamil infusion of 0.04 mg/kg/min × 1 h then 0.08 mg/kg/min × 1 h then 0.1 mg/kg/min until death</p> <p>– Hemodynamics: significant improvement in myocardial contractile function independent of glucose transport compared to normal saline</p>	<p>ARRIVE: 15/20</p> <p>NRCNA: 7/16</p>
Kline et al. (1993) ³⁹	<p>Group 1: NS</p> <p>Group 2: epinephrine</p> <p>Group 3: glucagon</p> <p>Group 4: HDI, 4 units/min ± dextrose and potassium</p>	<p>24 Mongrel dogs poisoned with verapamil infusion of 0.1 mg/kg/min until 50% reduction of MAP for 30 min, then infusion at 1 mg/kg/h until 4 h or death</p> <p>– Mortality: 6/6 in group 1, 2/6 in group 2, 3/6 in group 3, 0/6 in group 4 (significant)</p> <p>– Hemodynamics: improvement in groups 2 and 4</p> <p>– Adverse effects: increased lactate and hyperglycemia with epinephrine, hyperglycemia followed by hypoglycemia with glucagon</p>	<p>ARRIVE: 11/20</p> <p>NRCNA: 6/16</p>

Observational studies	STROBE and Thomas' tool	
Masson et al. (2012) ²²	ECLS (mean duration of 6 days \pm 2.9 days) vs not verapamil and diltiazem)	<p>– Mortality: 9/11 without ECLS compared to 23/41 with ECLS (patients in severe shock) and 0/7 without ECLS vs 3/3 with ECLS (patients in cardiac arrest) (significant difference)</p> <p>– Adverse effects: 4 limb ischemia, 1 inferior vena cava (IVC) thrombus and 2 cases of bleeding requiring surgical revision</p> <p>Institute of Health Economics tool for quality of case series and quality of reporting</p> <p>13/20 (2 unclear)</p> <p>STROBE: 17/22 Thomas tool:</p> <ul style="list-style-type: none"> • Strong: Selection bias • Moderate: Cohort methods, confounders, blinding, withdrawals, analysis • Weak: Data collection <p>Weak to moderate: Intervention integrity</p>
Case series		
Daubin et al. (2009) ¹¹¹	ECLS (mean duration of 4.5 days \pm 2.4 days)	<p>– Mortality: 4/17 deaths</p> <p>– Function: 13/17 survived without cardiovascular or neurologic sequelae</p> <p>– Adverse effects: 10 cannulation-related injuries, 6 limb ischemia with requirement for urgent revascularization in 3/6 (no more cases reported after arterial shunt was added to the cannulation technique), 1 femoral thrombus, 1 IVC thrombus, 2 bleeding at the cannulation site requiring surgical revision</p> <p>– Mortality: survival 50% at 24h and 25% at hospital discharge but not of the CCB poisoning survived</p> <p>– Function: survivors (3) were symptom-free without deficit at 1 year</p> <p>– LOS in ICU: 12–14 days</p> <p>– Adverse effects: none noticed</p> <p>– Mortality: 2/6</p> <p>– Adverse effects: limb ischemia (3/6), retroperitoneal hematoma 1/6</p> <p>retroperitoneal hematoma 1/6 doi:10.3109/15563650.2014.965827):</p>
Mégarbane et al. (2007) ¹¹²	ECLS (5–108 h, mean duration of 56 h)	<p>17 patients with persistent cardiac arrest or severe shock secondary to poisoning refractory to conventional therapy (4 CCB poisonings with verapamil)</p> <p>12 prolonged out-of-hospital cardiac arrests secondary to poisoning (2 CCB, verapamil)</p>
Babatasi et al. (2001) ¹¹³	ECLS (48–71 h, mean duration 59.25 \pm 2 h)	<p>6 cardiac arrests secondary to a cardiotoxic drug (2 CCB with verapamil)</p>
<p>Case reports (see online Appendix to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827):</p> <p>– Survival without neurologic or cardiac deficit reported in 7 cases^{156,180–182,185,187,189}</p> <p>– Death reported in 2 cases^{183,188}</p> <p>– Adverse effects: Bleeding in 1 case¹⁸³ and leg amputation reported in 1 case¹⁵⁶</p>		

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Extra-corporeal life-support (ECLS)

Table 1. (Continued)

Case series	Institute of Health Economics tool for quality of case series and quality of reporting
Konca et al. (2013) ⁴⁷	6/20 (2 unclear)
Supradip and Mrinal (2008) ⁴⁸	9/20 (13 unclear)
Karti et al. (2002) ⁴⁹	7/20 (5 unclear)
Howarth et al. (1994) ⁵⁰	9/20 (3 unclear)
Parikka et al. (1993) ⁵¹	3/20 (6 unclear)
Ramoska et al. (1993) ⁵²	10/20 (3 unclear)
Roper et al. (1993) ⁵³	3/20 (3 unclear)
Bausch et al. (1991) ⁵⁴	4/20 (5 unclear)
Horowitz and Rhee (1989) ⁵⁵	8/20 (4 unclear)
Henry et al. (1985) ⁵⁶	7/20 (3 unclear)
Jaeger et al. (1984) ²⁰	2/20 (6 unclear)
Case reports (see online appendix): - Improvement in hemodynamics reported in 19 cases ^{59,60,62-66,69,72,75,78,88} - No improvement in hemodynamics reported in 2 cases ^{74,77} - Adverse effects: Hypercalcemia reported in 1 case ⁷⁸	
Animal studies	ARRIVE guidelines and Modified NRCNA
Graudins and Wong (2010) ⁴⁰	ARRIVE: 16/20 NRCNA: 5/16
Graudins et al. (2008) ⁴¹	ARRIVE: 16/20 NRCNA: 5/16

Strubelt and Diederich (1990) ⁴²	<p>Group 1: NS Group 2: dopamine Group 3: norepinephrine Group 4: isoproterenol Group 5: polygeline Group 6: calcium chloride Group 1: calcium chloride Group 2: isoproterenol Group 3: atropine Group 4: epinephrine Group 5: norepinephrine Group 6: dopamine Group 7: phenylephrine Group 8: 4-AP</p>	31 Wistar rats (in 6 groups) poisoned with nisoldipine, 0.1 mg/kg/min	ARRIVE: 12/20 NRCNA: 5/16
Gay et al. (1986) ⁴³	<p>Group 1: NS Group 2: calcium chloride, 5 mg/kg/min Group 3: calcium chloride, 10 mg/kg/min Group 16: calcium chloride and isoproterenol</p>	23 Mongrel dogs poisoned with verapamil bolus, 0.72 mg/kg, followed by an infusion of 0.11 mg/kg/min	ARRIVE: 11/20 NRCNA: 6/16
Strubelt and Diederich (1986) ⁴⁴	<p>Rats: Group 1: NS Group 2: calcium chloride, 5 mg/kg/min Group 3: calcium chloride, 10 mg/kg/min Group 16: calcium chloride and isoproterenol</p>	95 Wistar rats (in 16 groups) poisoned with nifedipine, 0.5 mg/kg/min, and 21 bastard rabbits (in 5 groups) poisoned with nifedipine, 0.2 mg/kg/min	ARRIVE: 13/20 NRCNA: 4/16
Strubelt (1984) ⁴⁵	<p>Group 1: calcium Group 2: epinephrine Group 3: dopamine Group 4: norepinephrine Groups 5-6: isoproterenol Group 7: orciprenaline Group 8: prenalterol Group 9: angiotensin amide Group 10: atropine Group 11: haemacel</p>	80 Wistar rats (in 11 groups) poisoned with verapamil, 0.15 mg/kg/min	ARRIVE: 11/20 NRCNA: 5/16
Wesseling et al. (1983) ¹⁰⁵	<p>Group 1: NS Group 2: calcium levulate, 0.4 ml of 10% Group 3: 4-aminopyridine, 1 mg/kg, after the drop in SBP</p>	12 rabbits (in 3 groups) poisoned with verapamil, 30 mg/kg/h, until the SBP drops by one-third	ARRIVE: 10/20 NRCNA: 7/16

(Continued)

Table 1. (Continued)

Case series	Institute of Health Economics tool for quality of case series and quality of reporting
Vick et al. (1983) ⁴⁶	ARRIVE: 5/20 NRCNA: 3/16
Rabbits: calcium chloride, 300 mg/kg, after the verapamil infusion Pigs: 150 mg/kg after the verapamil infusion	- Hemodynamics: calcium chloride restored blood pressure but not heart rate
42 rabbits (12 in treatment group) poisoned with verapamil, 0.1 mg/kg/min, for 15 min preceded by propranolol, 1 mg/kg, and 13 pigs (5 in treatment group) poisoned with verapamil, 0.5 mg/kg, preceded by propranolol, 0.5 mg/kg	
Levine et al. (2013) ⁸²	Mortality: 1/48 - Adverse effects: 8 ischemic complications in 5 patients, 3 cardiac arrests before the use of vasopressors - Mortality: 1/4
Vasopressors	
48 patients poisoned with verapamil or diltiazem	
Konca et al. (2013) ⁴⁷	6/20 (2 unclear)
Dopamine	
4/7 poisoned with CCB on dopamine	
Kanagarajan et al. (2007) ⁸⁰	9/20 (3 unclear)
Vasopressin, 2.4–4.8 units/h	
2 poisoned with amlodipine and verapamil sustained-release	
Groszek et al. (2003) ⁸⁴	2/20 (4 unclear)
Dopamine	
2 poisoned with nifedipine	
Karti et al. (2002) ⁴⁹	7/20 (5 unclear)
Dopamine	
2 poisoned with verapamil SR	
Ramoska et al. (1993) ⁵²	10/20 (3 unclear)
Dopamine, isoproterenol	
113 poisoned with verapamil, diltiazem, or nifedipine (10 received vasopressors)	
Parikka et al. (1993) ⁵¹	4/20 (5 unclear)
Dopamine, dobutamine, epinephrine, isoproterenol	
7 poisoned with diltiazem, verapamil, or nifedipine	
Howarth et al. (1994) ⁵⁰	9/20 (3 unclear)
Dopamine, adrenaline	
15 poisoned with verapamil, diltiazem, or nifedipine	
Jaeger et al. (1990) ⁵⁷	2/20 (6 unclear)
Dopamine, metaraminol	
3 poisoned with diltiazem	
Sauder et al. (1990) ²⁷	3/20 (4 unclear)
Dopamine except 1 patient had epinephrine	
6 poisoned with verapamil	

Case reports (see online Appendix to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827>):
 - Improvement in hemodynamics reported in most reported cases^{72,81,85,119,191,192-194} except 2^{190,195}
 - Adverse effects: None reported

Animal studies	ARRIVE guidelines and Modified NRCNA
<p>Engelbretsen et al. (2010)³⁶</p> <p>Group 1: NS Group 2: HDI, 2 units/kg/h, increased Q10 min 2 units/kg/h ad max Group 3: HDI and phenylephrine</p> <p>15 Yorkshire pigs poisoned with nifedipine, 0.0125 mg/kg/min, until 25% of baseline MAP X CO</p>	<p>ARRIVE: 18/20 NRCNA: 8/16</p> <p>- Mortality: 4/5 deaths in group 1, 1/5 in group 2, and no death in group 3 - Hemodynamics: significant improvement in MAP compared to group 1 and no significant difference in hemodynamics between groups 2 and 3, the addition of phenylephrine did not make a difference - Adverse effects: hypoglycemia and hypokalemia - Mortality: 4/8 in the vasopressin group vs 2/10 in the control group ($p = 0.32$) - Hemodynamics: no significant improvement in MAP, cardiac output, or systemic vascular resistance</p>
<p>Barry et al. (2005)⁷⁹</p> <p>Group 1: NS Group 2: vasopressin, 0.01 units/kg/min</p> <p>18 swine (9 per group)</p>	<p>ARRIVE: 18/20 NRCNA: 9/16</p> <p>- Mortality: 0/6 in the vasopressin group vs 2/6 in the control group - Hemodynamics: no significant difference</p>
<p>Sztajnkrycyer et al. (2004)²²⁸</p> <p>Group 1: NS Group 2: vasopressin, 0.004 units/kg/min, increasing to 0.01 units/kg/min then 0.04 units/kg/min Q 20 min</p> <p>12 dogs (6 per group)</p>	<p>ARRIVE: 15/20 NRCNA: 6/16</p> <p>- Mortality: 2/6 deaths in group 1 vs none in the other groups - Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2-3 - Mortality: 2/6 deaths in group 1 vs none in the other groups - Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2-3 - Adverse effects: increased lactate and glycemia with epinephrine</p>
<p>Stone et al. (1996)⁸⁶</p> <p>Group 1: NS Group 2: glucagon Group 3: glucagon and phenylephrine, 100-180 µg/min</p> <p>18 Mongrel dogs (6 per group)</p>	<p>ARRIVE: 15/20 NRCNA: 6/16</p> <p>- Mortality: 2/6 deaths in group 1 vs none in the other groups - Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2-3</p>
<p>Kline et al. (1993)³⁹</p> <p>Group 1: NS Group 2: epinephrine Group 3: glucagon Group 4: HDI, 4 units/min</p> <p>24 Mongrel dogs</p>	<p>ARRIVE: 11/20 NRCNA: 6/16</p> <p>- Mortality: 2/6 deaths in group 1 vs none in the other groups - Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2-3 - Adverse effects: increased lactate and glycemia with epinephrine</p>
<p>Strubelt and Diederich (1990)⁴²</p> <p>Group 1: NS Group 2: dopamine Group 3: norepinephrine Group 4: isoproterenol Group 5: polygeline Group 6: Calcium chloride</p> <p>31 Wistar rats (in 6 groups) poisoned with nisoldipine, 0.1 mg/kg/min</p>	<p>ARRIVE: 12/20 NRCNA: 5/16</p> <p>- Mortality: 135% improvement in survival in group 2 (129.2 min vs 54.7 min +/- 11.1 min), 75.6 min vs 54.7 min in group 3, 187% improvement in group 4 (157 min vs 54.7 min) - Hemodynamics: groups 2-4 showed an increase in blood pressure, cardiac output and stroke volume, group 3 showed an increase in resistances - Epinephrine, norepinephrine, dopamine, and high doses of phenylephrine increase cardiac output; AO and LV dp/dt increased</p>
<p>Gay et al. (1986)⁴³</p> <p>Group 1: calcium chloride Group 2: isoproterenol Group 3: atropine Group 4: epinephrine Group 5: norepinephrine Group 6: dopamine Group 7: phenylephrine Group 8: 4-AP</p> <p>23 Mongrel dogs poisoned with verapamil bolus, 0.72 mg/kg, followed by an infusion of 0.11 mg/kg/min</p>	<p>ARRIVE: 11/20 NRCNA: 6.5/16</p> <p>- Mortality: 2/6 deaths in group 1 vs none in the other groups - Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2-3 - Adverse effects: increased lactate and glycemia with epinephrine</p>

Vasopressors

(Continued)

Table 1. (Continued)

Strubelt and Diederich (1986) ⁴⁴	Group 1: NS Group 2: calcium chloride, 5 mg/kg/min Group 3: calcium chloride, 10 mg/kg/min Group 16: calcium chloride and isoproterenol Rabbits: Group 1: NS Group 2: calcium chloride Group 5: calcium chloride and isoproterenol	95 Wistar rats (in 16 groups) poisoned with nifedipine, 0.5 mg/kg/min, and 21 bastard rabbits (in 5 groups) poisoned with nifedipine, 0.2 mg/kg/min	– Mortality: 100% improvement with calcium, isoproterenol, or dopamine in rats, survival also improved with calcium in rabbits, but not with isoproterenol or dopamine; 50% improvement after epinephrine and norepinephrine – Hemodynamics: improvement in cardiac output and blood pressure with most of the vasopressors	ARRIVE: 13/20 NRCNA: 4/16
Strubelt (1984) ⁴⁵	Group 1: calcium Group 2: epinephrine Group 3: dopamine Group 4: norepinephrine Groups 5-6: isoproterenol Group 7: orciprenaline Group 8: prenalterol Group 9: angiotensin Group 10: atropine Group 11: haemacel	80 Wistar rats (in 11 groups) poisoned with verapamil, 0.15 mg/kg/min	– Mortality: tripled with epinephrine, dopamine, norepinephrine, isoproterenol, and orciprenaline – Hemodynamics: sympathomimetics increased the blood pressure, heart rate and cardiac output; epinephrine and isoproterenol antagonized the decrease in LC dp/dt max	ARRIVE: 11/20 NRCNA: 5/16

Vasopressors

HDI, high-dose insulin.

increasing lactate were noted as adverse effects.³⁹ Dopamine and norepinephrine infusions showed improved survival and hemodynamics in animal studies,^{42,45} but results were inconsistent in case series.^{27,49–52,57,82–84} No significant ischemic complications were noted with high doses of vasopressors in a case series of 48 patients.⁸² In animal studies, the use of isoproterenol^{43–45,51,52} or atropine^{43,45} showed occasional improvement in hemodynamics. In one human case series of three patients⁵⁷ and one case report,⁸⁵ patients who received isoproterenol had improved heart rate and blood pressure.

Glucagon

Improvement in heart rate and cardiac output was observed with glucagon (IV bolus of 3 mg, followed by an infusion of 3 mg/h) in two of three animal studies,^{86,87} but in only one⁸⁸ of the three human case series.^{48 53,84} Cardiac output was not measured in case series. Hyperglycemia and vomiting were side effects observed in six case reports.^{73,78,89–92}

Lipid emulsion therapy

In an animal model^{95–97} of IV verapamil toxicity, the administration of 20% lipid emulsion (IV bolus of 6.2–18.6 ml/kg) was associated with improvement in hemodynamics and survival. However, there was no significant improvement or an increased mortality in two animal studies using an oral verapamil toxicity model.^{93,94} One available human case series⁹⁰ (five patients) demonstrated 60% mortality when using this antidote compared to a lower mortality reported in retrospective studies of CCB poisoning (6% reported by St-Onge et al. in 2012²). Importantly, the mortality reported in observational studies with this treatment included CCB ingestions regardless of severity, whereas the case series published by Geib et al.⁹⁸ only included severe cases. In one case report,⁹⁹ adverse effects such as hypertriglyceridemia and hypoxemia were observed with lipid emulsion when used at exceptionally high doses (2 L). Hyponatremia, extreme lipemia, and inability to obtain reliable complete blood count, arterial blood gas, or electrolyte levels were also noted in one case report.⁹³

4-Aminopyridine

Animal studies^{40,43,100–105} and human case series^{106,107} showed survival and hemodynamic benefit with 4-aminopyridine. Seizures were observed in two animal studies^{101,102}

Levosimendan

Animal studies^{40,108,109} and a small case series¹¹⁰ suggested a hemodynamic benefit for levosimendan, although seizures were observed in both patients.¹¹⁰ One of four animal studies¹⁰⁸ used higher doses of verapamil to induce toxicity, resulting in increased mortality.

Results of individual studies and risks of bias for mechanical interventions

Extracorporeal life support

The use of extracorporeal life support was associated with a survival benefit in patients with severe shock or cardiac arrest

secondary to cardiotoxic poisonings. In the observational study published by Masson et al.,²² extracorporeal life support was associated with a lower mortality when initiated in a group of 14 patients compared to conventional therapies provided to a group of 48 patients (48% vs. 86%) after adjustment for Simplified Acute Physiology Score (SAPS) II and beta-blocker intoxication. Most human case series reported positive functional outcomes in the majority of survivors.^{111,112} However, some patients experienced limb ischemia (10% in the observational study²² and 0–50% in the case series^{111–113}), thrombosis (2% in the observational study²² and 0–12% in the case series^{111–113}), or hemorrhage (5% in the observational study²² and 0–12% in the case series^{111–113}).

Pacemaker

Results were inconsistent on the success of temporary pacemakers in achieving capture and improving hemodynamics in human case series^{52,114–118} and case reports.^{119–121} Pacing and capture problems were identified even with transvenous pacemakers.^{114–116} However, hemodynamic improvement was observed most of the time when capture was successful^{116,118–120} and no adverse effect has been reported.

Results of individual studies and risks of bias for interventions for which only small case series, case reports, or animal studies are available

The use of amrinone did not show a benefit in animal studies,^{122,123} although human case reports using another phosphodiesterase inhibitor (enoximone) observed an increase in inotropy and a decrease in vasopressor requirement.^{124,125} One human case series¹²⁶ and two case reports^{127,128} suggested use of plasma exchange to decrease verapamil concentrations and improve hemodynamics. One human case series of three patients¹²⁹ and one case report¹³⁰ suggested the use of extracorporeal albumin dialysis to improve hemodynamics without a clear impact on the serum CCB concentrations. Only human case reports were found for charcoal hemoperfusion;¹³¹ continuous venovenous hemodiafiltration;^{132–135} insertion of an intra-aortic balloon pump,¹³⁶ Impella device,¹³⁷ and methylene blue.^{138–140} Animal studies showed conflicting results for the use of carnitine.^{153–155} Finally, only animal studies were found for the following interventions: Bay K 8644 and CGP 28932,^{100,101,103} digoxin,^{141–143} cyclodextrin,^{144,145} suggamadex,¹⁴⁶ liposomes,^{147,148} bicarbonate,¹⁴⁹ fructose 1,6-diphosphate,¹⁵⁰ PK11195¹⁵¹ and triiodothyronine.¹⁵²

Synthesis of results

Mortality

High-dose insulin^{20,21} (IV bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) initiated before or shortly after vasopressors was associated with survival improvement. In animal studies (rats and rabbits), calcium,^{40–42,44,45,48–50,56} epinephrine,⁴⁵ dopamine,^{27,42,44,45,49,84} norepinephrine,^{42,45} and 4-aminopyridine^{40,43,100,102–104} were associated with reduced

mortality. Based on human case series, only calcium^{48–50,56} and dopamine^{27,49,84} were associated with reduced mortality. Most human studies did not report a survival benefit with atropine,^{45,50,53} glucagon,^{39,53} pacemaker,¹¹⁷ levosimendan,¹⁰⁸ or plasma exchange.¹²⁶ Animal studies did not report any survival benefit either with atropine in a rat model,⁴⁵ glucagon in a dog model,³⁹ or levosimendan in a rat model.¹⁰⁸ Animal studies (two murine models^{95,96} and one dog model,⁹⁷ all of them of moderate methodological quality) suggested that lipid emulsion improves survival in an IV model of verapamil poisoning. That was not confirmed in two oral models of verapamil poisoning.^{93–94} Extracorporeal life support²² for patients with cardiac arrest or severe shock refractory to conventional therapy reported a benefit in survival. Two patients survived with albumin dialysis,^{129,130} and only animal studies supported the use of Bay K8644.^{100,101,103}

Hemodynamics

Positive effects on hemodynamics were documented with the use of high-dose insulin in human observational studies,²¹ case series,^{23,33–35} and animal studies (pigs and dogs).^{35–37} Also, extracorporeal life support in human studies,^{22,111–113} calcium in most animal studies (rodents and dogs),^{40–46} and some human case series reported improvement in hemodynamics.^{52,56} Animal studies on the effects of epinephrine, dopamine, and norepinephrine in rats^{42,45} and dogs⁴³ also demonstrated an improvement in hemodynamics. The same effects were documented for 4-aminopyridine in five different types of animal,^{43,102–105} for lipid emulsion in an IV but not an oral model of verapamil toxicity,^{93–95} and for Bay K8644 in rodents.^{100,101,103} The variability in hemodynamic response to calcium observed in human case series^{48–50,52,55} was also seen with atropine,^{50,52} glucagon,^{39,48} and pacemakers.^{52,114–116} Hemodynamic improvement was reported with levosimendan in two patients¹¹⁰ and animals.^{30,40} Digoxin was associated with hemodynamic improvement in dogs,^{141–143} but an inconsistent effect on mortality. Animal studies showed an improvement in blood pressure with the use of liposomes,^{147,148} but this treatment was not tested in humans. The effect of decontamination^{25–29,54} on the prevention of toxicity in humans poisoned with CCB was limited to small biased case series.

Impact on functional outcomes

Functional outcomes were only reported in two case series involving extracorporeal life support in humans. Daubin et al.¹¹¹ observed that all survivors in their sample ($n = 3$) were discharged without cardiovascular or neurological sequelae. Mégarbane et al.¹¹² reported that three patients treated with extracorporeal life support were symptom-free after one year. However, in isolated case reports, one patient was discharged to a long-term care facility³⁷ and another underwent leg amputation.¹⁵⁶

Impact on other outcomes

Only one observational study concerning high-dose insulin studied the impact on LOS in ICU or hospital, but did not find significant differences in patients who received the therapy.¹⁹ However, no power calculation was done.

Risk of bias across studies

Observational studies

The interobserver agreement on the STROBE checklist scoring was excellent for observational studies (kappa: 0.90; 95% CI: 0.82–0.99). Percent agreement for each element varied from 67 to 100%, with the exception of the criterion related to the mention of a specific hypothesis, on which observers frequently disagreed. The high-dose insulin studies reported between 4 and 10 of 22 elements in the STROBE checklist, while the extracorporeal life support study reported 17 of 22. Clear eligibility criteria and reports of data collection methods for high-dose insulin studies, sample size calculation, statistical methods, reported bias, and limitations were often missing from observational studies. The application of the Thomas tool resulted in 67% or higher agreement. However, observers disagreed on selection bias and data quality. Relevant confounders such as comorbidities were poorly described in all studies. Adherence to the high-dose insulin protocol was often variable. Therefore, the integrity of the intervention (defined as the degree to which it is implemented as planned or intended) was considered weak for high-dose insulin.

Case series

The interobserver agreement with the Institute of Health Economics tool for Quality of Case Series and Quality of reporting was substantial (kappa: 0.80; 95% CI: 0.76–0.84). Percent agreement was higher than 88% when judging the quality of the statistical tests used (which were generally descriptive) and follow-up rates. Case series scored 10/20 or less except for two of three articles involving extracorporeal life support (13/20 and 15/20), one of four high-dose insulin case series scored 13/20, and one of ten vasopressors case series scored 14/20. It was often unclear whether several case series were collected in different centers, or participants were recruited consecutively, or there was loss to follow-up. A very small number of studies were conducted prospectively with outcomes measured *a priori* and with adverse events reported.

Animal studies

The interobserver agreement for the use of the ARRIVE guidelines for animal studies was excellent (kappa: 0.90; 95% CI: 0.88–0.92). Percent agreement for each item varied from 80 to 100%. All studies obtained a score of 10/20–18/20 except for one related to calcium use (5/20), two related to lipid emulsion (7/20–8/20), and one related to carnitine (8/20). The studies' relevance to human biology was unclear and details concerning the randomization procedure, sample size calculation, and husbandry conditions were often missing. When using the modified NRCNA list, the interobserver agreement was still excellent (kappa: 0.98; 95% CI: 0.96–0.99) and the percent agreement remained higher than 88% for all items. All studies obtained a score between 4/16 and 9/16. The weaknesses identified by the NRCNA list included use of unanesthetized animals, lack of blood concentration measurements, intervention tested

in only one species, oral CCB administration, autopsy not conducted, lack of allocation concealment, and blinded assessment.

As expected, the risk of bias with case reports was high. Risk of bias across studies was high for all interventions and high to moderate for extracorporeal life support. Appendix 4 (to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827>) lists risk of bias across studies for each intervention. The risk of publication bias was estimated to be high, considering inherent risk with case reports.

Limitations

The evidence for treatment of CCB poisoning derives from a highly biased and heterogeneous literature. Important limitations were identified in the majority of studies. Different analysis tools have been used to assess the risk of bias with transparency, but to our knowledge this is the first time that these tools have been used in toxicology. For many interventions (high-dose insulin, extracorporeal life support, calcium, dopamine, norepinephrine, epinephrine, and 4-aminopyridine), results were consistent across different study types. Inconsistency among studies arose from differences in interventions, populations, and outcome measures. Moreover, head-to-head comparisons of treatments were infrequent, making it difficult to evaluate the comparability of treatments. Based upon the published literature, few valid inferences can be drawn about the relative merits of one intervention over another.

The search strategy was designed to be as inclusive as possible, including a search of the gray literature. Some articles identified by title could not be retrieved, but these were primarily case reports and it is unlikely that they would have influenced the overall findings.

Conclusions

This systematic review found a low level of evidence supporting the use of high-dose insulin and extracorporeal life support, and a very low level of evidence supporting the use of calcium, dopamine, norepinephrine, and epinephrine for the treatment of CCB poisoning. This systematic review focused on important outcomes for decision-making in managing patients poisoned with CCB. Controlled clinical trials involving vasopressors, calcium, high-dose insulin, and extracorporeal life support should be performed.

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Supplementary material available online

Supplementary Appendices 1–4.