**APPENDIX 1 (online): Additional information concerning calcium channel blocker poisoning**

In 2014, the American National Poison Data System (1) reported 102,170 human exposures to cardiovascular drugs with a mean increase in serious exposures of 988 cases per year. Cardiovascular drugs are the second category of substance associated with the largest number of poisoning fatalities (1). In 2014, calcium channel blockers (CCBs) were responsible of 74 deaths in United States (1). A retrospective study conducted in a Canadian province (2) reported a mortality of 6% and complications in 50% of patients including acute renal failure (35%), metabolic acidosis (25%), acute pulmonary oedema (15%), aspiration pneumonia (15%), rhabdomyolysis (8%), myocardial ischemia (7%), abnormal liver function tests (6%), cerebral anoxia (4%) and ileus (3%).

Available calcium channel blockers include the dihydropyridines and non-dihydropyridines. Dihydropyridines preferentially block calcium channels in vascular smooth muscle causing hypotension. Dihydropyridines have lower affinity for myocardial calcium channels, but this lessens at higher doses (10, 11). In some overdoses, reflex tachycardia may be encountered. However, in addition to their peripheral effects causing hypotension, non-dihydropyridines cause bradycardia by inhibiting L-type calcium channels in the sinoatrial and atrioventricular nodes (6). Pharmacokinetics vary among the CCBs which are available in different formulations (7), and may be altered by coingestants, pharmacobezoar formation, ileus, or impaired perfusion due to shock, or vasopressor administration (8, 9).

Therefore, in order to manage CCB poisoning adequately, it is important to take into account the time of ingestion, the type and formulation of CCB ingested, the dose and the co-ingestants. Poison control centres can help to evaluate the risk and guide healthcare professionals in patient care.

**APPENDIX 2 (online) : Additional information regarding material and methods**

**SELECTION OF THE WORKGROUP MEMBERS**

We created a workgroup representing a diverse group of participating international healthcare organizations (Table 1). Critical care, toxicology and emergency medicine associations representing North America and Europe were invited to participate. The Canadian Association of Poison Control Centres (CAPCC) acted as the leading association, named a chair and a co-chair, and a representative was appointed by each participating organization based on their respective internal selection process. Most of the workgroup members are active clinician-scientists. Each workgroup member completed the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest (COI) and was aware of others’ researches and publications. No relevant COI was identified and the workgroup members felt that all members could vote on all recommendations.

**THE EVIDENCE**

As a starting point, the workgroup used an existing systematic review (16) that examined the effects of all interventions on the outcomes targeted by our recommendations up to December 31, 2013 (see Appendices 3-5) (16).

The articles included in the evidence that was assessed for the voting process included the evidence in the systematic review published in 2014 and articles found using the same search strategy up to December 2014 (17-21).

Following the votes and the expert consensus, the same strategy was used to retrieve new articles up to May 1st 2016. The literature was presented to the workgroup. The majority of members decided that no new evidence warranted a new voting process. Between the votes and May 2016, only a few animal studies (22-24), case reports (25-31) and a small cases series (32) were published.

**RECOMMENDATIONS STATEMENTS**

The workgroup was divided in three subgroups, each of which was responsible for a specific intervention and which presented a summary outlining the evidence in detail, including the benefits and risks. The subgroups proposed statements that were used for the subsequent modified Delphi process after discussion with the other workgroup members.

Each statement was associated with a specific level of evidence, which was determined using the GRADE (14) system (Table 2). In order to determine the strength of recommendation (Table 2), the workgroup proceeded to a modified Delphi method (four rounds of anonymous online votes using a 9-point Likert scale, followed by telephone meetings and a face-to-face meeting held in Brussels in May 2014). During the first round, the workgroup agreed on which definitions and clinical categories would be used (Appendix 6). The workgroup members voted on the proposed statements during the second and third rounds. At the third round, the strength of recommendation for each statement (Table 2) was determined by the results of the votes using the medians, the lower/upper quartiles, and the disagreement indices (RAND/UCLA Appropriateness Method) (15) as described in Figure 2. A fourth round of Delphi was used to try to prioritize first line treatments.

**VALUES AND PREFERENCES**

The perceived influence of the workgroup values and preferences on the vote results were documented at each round. In order to consider values and preferences of decision makers, clinicians, patients and relatives, the draft recommendations were posted on a blog for between October 13th and October 27th 2014 for public comment (16). The public was asked to provide comments. In order to encourage participation, messages were posted on social media websites of relevant organizations of patients and relatives, poison control centers, and professional organizations (33). All comments were communicated to the workgroup, which modified the manuscript accordingly when doing so improved clarity.

The members reported the following factors as influencing their vote the most (≥6/9 on a Likert scale): 1) the evidence (8/9); 2) the balance between risks and benefits (7/9); 3) the feasibility and applicability of the intervention (7/9) and; 4) their experience and training (7/9). In terms of public involvement, the blog (<http://poisoningsguidelines.com>) documented 796 visitors from 61 countries during the period the draft of recommendations were posted for public feedback. Suggestions were made to clarify statements and facilitate its application, but no disagreement was expressed.

**INTERNAL AND EXTERNAL REVIEWS**

The recommendations were submitted to all participating associations for internal review and to anonymous reviewers chosen by the associations for external review. The external reviewers evaluated the recommendations with the AGREE tool (13). The three external reviewers gave a global score of 6/7 to the recommendations development process. The main suggestions for improvement concerned the need for more implementation tools and a better defined update process.

Most of the participating organizations endorsed the recommendations after the internal review process, except two that will not be mentioned in this manuscript (one requested not to be mentioned and the other one was notably in disagreement with other associations’ suggestions and requests) (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/C96). The workgroup clarified some statements and the fact that first line treatments should be prioritized based on desired effect to facilitate their application. Questions raised by the reviewers that could not be answered with the current evidence are noted in areas for future research.

A second face-to-face meeting was held in New Orleans in October 2014 to discuss the documented values, preferences, and the preliminary results of the internal and external reviews.

**IMPLEMENTATION AND APPLICABILITY**

Because effective implementation strategies include multifaceted interventions, interactive education and clinical reminder systems (34), we intend to post the algorithm on our blog where a checklist, and a quiz will be available. The blog link (<http://poisoningsguidelines.com>) will be sent to all relevant associations and training programs. Interventions that are not widely available, such as VA-ECMO (or ECLS), or those that are not performed on a regular basis by non-toxicologists may still be difficult to integrate into practice. Therefore, associations must use proactive knowledge translation strategies such as educational meetings and workshops.

To monitor the impact of the guideline implementation, the workgroup plans to conduct a survey two years post implementation. Decision makers should consider monitoring adherence to recommendations and outcomes.

**PLANNED REVISIONS**

These guidelines will be updated if there is a significant change in the evidence or, in the alternative, every five years. Comments and suggestions will be collected on the workgroup’s blog in future revisions, and studies will be conducted to monitor adherence to the current guidelines.

**APPENDIX 3 (online): Inclusion criteria for the systematic review**

Type of study subjects (P = population): Studies involving adult, children or animals poisoned with CCBs were eligible.

Type of intervention and comparison (I = intervention; C = comparison): Any treatment and type of comparison were eligible as long as outcome measures were reported.

Type of outcome measures (O = outomes): Outcomes included mortality (survival to discharge for human studies or LD50 or survival for animal studies), functional outcomes (defined as a return to functional baseline), and duration of intensive care unit stay or hospitalization. Intermediate outcomes included prevention of or attenuation of toxicity, a decrease in CCB serum level, improved hemodynamics and a decrease in duration of vasopressor use. Adverse effects were documented in the previously mentioned systematic review (16). Since costs were not reported, two workgroup members conducted a cost-effectiveness analysis with other co-authors concerning the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO), the most expensive and invasive intervention (36).

Type of studies (S = studies): We considered systematic reviews, controlled trials, observational studies, case series and animal studies were considered to evaluate the effect of each intervention on outcomes (first three questions in Figure 1). To address the fourth key question, we examined any study that could identify an association between the intermediate outcomes and patient-centered health outcomes. Therefore, we included only controlled trials and observational studies. To answer the fifth key question, case reports were considered in addition to other types of evidence.

**APPENDICE 4 (online): Flow diagram and search strategy**

* Reproduced with permission from: St-Onge et al., 2014*16

Searched conducted for the systematic review that pre-dated the establishment of this workgroup (16):

We searched Medline/OVID, Pubmed, EMBASE, Cochrane Library, Toxline and International pharmaceutical abstracts up to December, 2013 (inclusively) without time restrictions. Two librarians developed the search strategy with 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]. We also searched conference proceedings and meeting abstracts of the EAPCCT and NACCT (2008-2013), trial registries and Google Scholar. Authors of selected publications (except for case reports) were contacted. Please see the example of search strategy for Medline/OVID. A list of excluded article is available on demand.

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>**

--------------------------------------------------------------------------------

1 exp Calcium Channel Blockers/ae, po, to [Adverse Effects, Poisoning, Toxicity]

2 exp Calcium Channel Blockers/

3 exp Drug Overdose/

4 exp Medication Errors/

5 exp Poisoning/

6 3 or 4 or 5

7 2 and 6

8 1 or 7

9 overdose\*.tw.

10 poisoning.tw.

11 toxicity.tw.

12 "adverse effect\*".tw.

13 medication error\*.tw.

14 or/9-13

15 calcium channel antagonist\*.tw.

16 (Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxins or Diltiazem 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 Perhexiline or Prenylamine or Verapamil).tw.

17 Calcium Channel Blocker\*.tw.

18 or/15-17

19 14 and 18

20 8 or 19

21 limit 20 to yr="1946 - 2012"

22 limit 21 to yr="2012"

23 limit 22 to ed=20120101-20120810

24 limit 20 to yr="1946 - 2011"

25 23 or 24

26 limit 25 to (comment or editorial or letter)

27 25 not 26

28 limit 27 to "all child (0 to 18 years)"

29 limit 28 to "all adult (19 plus years)"

30 28 not 29

31 27 not 30

32 from 31 keep 1-6000

33 remove duplicates from 32

34 from 31 keep 6001-8193

35 remove duplicates from 34

36 33 or 35

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

**APPENDIX 5 (online): Number of articles reporting each outcome per intervention** (unpublished results from St-Onge et al., 2014 (16) and updated literature up to May 2016 (22-32))

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Intervention** | **Observational studies**N = number of articles(number of patients) | **Case series**N = number of articles(number of patients) | **Case reports**N = number of articles and patients | **Animal studies**N = number of articles (number of animals) | **Total number****of articles** |
| **High-dose insulin** | **3 (73 patients)** | **6 (60 patients)** | **22** | **4 (77 animals)** | **35** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes- Adverse effects | 2 (53 patients)2 (27 patients)-2 (27 patients)1 (7 patients) | 5 (58 patients)5 (15 patients)1 (2 patients)2 (8 patients)4 (57 patients) | 18151103 | 2 (39 animals)4 (77 animals)--2 (39 animals) | 272621410 |
| **Extracorporeal life support** | **1 (62 patients, 16 CCBs)** | **3 (35 patients, 8 CCBs)** | **9** | **0** | **13** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes- Adverse effects | 1 (62 patients, 16 CCBs)---1 (62 patients, 16 CCBs) | 3 (35 patients, 8 CCBs)-2 (29 patients, 6 CCBs)1 (12 patients, 2 CCBs)3 (35 patients, 8 CCBs) | 97631 | ----- | 137845 |
| **Calcium \*** | **0** | **11 (168 patients)** | **20 (1)** | **8 (378 animals)** | **39 (1)** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes- Adverse effects | ----- | 9 (44 patients)7 (136 patients)-1 (2 patients)1 (11 patients) | 1716262 | 6 (313 animals)7 (366 animals)--- | 3230273 |
| **Vasopressors** | **0** | **10 (205** patients) | **10** | **9 (316 animals)** | **29** |
| - Mortality- Hemodynamics- Other outcomes- Adverse effects | ---- | 9 (92 patients)8 (152 patients)1 (2 patients)1 (48 patients) | 7981 | 8 (293 animals)9 (316 animals)-2 (39 animals) | 242694 |
| **Decontamination** | **0** | **8 (620 patients)** | **2** | **0** | **10** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes- Adverse effects | ----- | 7 (614 patients)3 (13 patients)1 (2 patients)-2 (180 patients) | 2--1- | ----- | 93112 |
| **Pacemaker \*\*** | **0** | **5 (13 patients)** | **2 (1)** | **0** | **7 (1)** |
| - Mortality- Hemodynamics- Other outcomes | --- | 4 (9 patients)5 (13 patients)- | 221 | --- | 671 |
| **Lipid emulsion** | **0** | **2 (17 patients)** | **45** | **8 (161 animals)** | 55 |
| - Mortality- Hemodynamics- Functional outcomes- Adverse effects | ---- | 2 (17 patients)2 (17 patients)2 (17 patients)1 (15 patients) | 4545-5 | 8 (161 animals)6 (119 animals)-- | 555325 |

No controlled trials were found. Some studies evaluated more than one outcome.

\*1 case report full text articlenot found (not included in appendix 3)

\*\*1 case report full text article not found (not included in appendix 3)

\*\*\*3 case reports full text article not found (not included in appendix 3)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Intervention** | **Observational studies**N = number of articles(number of patients) | **Case series**N = number of articles(number of patients) | **Case reports**N = number of articles and patients | **Animal studies**N = number of articles (number of animals) | **Total number****of articles** |
| **Glucagon** | **0** | **2 (5 patients)** | **10** | **3 (51 animals)** | **15** |
| - Mortality- Hemodynamics- Other outcomes- Adverse effects | ---- | 2 (5 patients)2 (5 patients)1 (2 patients)- | 10646 | 3 (51 animals)3 (51 animals)-- | 151156 |
| **Atropine** | **0** | **0** | **0** | **2 (103 animals)** | **2** |
| - Mortality- Hemodynamics | -- | 00 | -- | 2 (103 animals)2 (103 animals) | 22 |
| **Plasma exchange \*\*\*** | **0** | **1 (2 patients)** | **3 (4)** | **0** | **4 (5)** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes | ---- | 1 (2 patients)1 (2 patients)-1 (2 patients) | 3212 | ---- | 4313 |
| **Levosimendan** | **0** | **1 (2 patients)** | **3** | **4 (121 animals)** | **8** |
| - Mortality- Hemodynamics- Other outcomes- Adverse effects | ---- | 1 (2 patients)1 (2 patients)1 (2 patients)1 (2 patients) | 333- | 4 (121 animals)3 (107 animals)-- | 8741 |
| **4-aminopyridine or 3,4-diaminopyridine** | **0** | **2 (3 patients)** | **0** | **8 (148 animals)** | **10** |
| - Mortality- Hemodynamics- Other outcomes- Adverse effects | ---- | 2 (3 patients)2 (3 patients)2 (3 patients)- | ---- | 8 (148 animals)8 (148 animals)-1 (18 animals) | 101021 |
| **Albumin dialysis or MARS** | **0** | **1 (3 patients)** | **3** | **0** | **4** |
| - Mortality- Hemodynamics- Other outcomes- Functional outcomes- Adverse effects | ----- | 1 (3 patients)1 (3 patients)-1 (3 patients)- | 33111 | ----- | 44121 |
| **Charcoal hemoperfusion** | **0** | **0** | **6** | **0** | **4** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes | ---- | ---- | 5524 | ---- | 3424 |
| **Dialysis** | **0** | **0** | **5** | **0** | **3** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes | ---- | ---- | 5121 | ---- | 3121 |

No controlled trials were found. Some studies evaluated more than one outcome.

\*1 case report full text articlenot found (not included in appendix 3)

\*\*1 case report full text article not found (not included in appendix 3)

\*\*\*3 case reports full text article not found (not included in appendix 3)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Intervention** | **Observational studies**N = number of articles(number of patients) | **Case series**N = number of articles(number of patients) | **Case reports**N = number of articles and patients | **Animal studies**N = number of articles (number of animals) | **Total number****of articles** |
| **Intra-aortic balloon pump** | **0** | **0** | **2** | **0** | **2** |
| - Mortality- Hemodynamics- Functional outcomes- Other outcomes | ---- | ---- | 2222 | ---- | 2222 |
| **Methylene blue** | **0** | 0 | 10 | 1 (30 animals) | 11 |
| - Mortality- Hemodynamics- Functional outcomes | --- | --- | 10105 | 1 (30 animals)1 (30 animals)- | 11115 |
| **Carnitine** | **0** | **0** | **1** | **3 (70 animals)** | **4** |
| - Mortality- Hemodynamics | -- | -- | 11 | 3 (70 animals)3 (70 animals) | 44 |
| **Sugammadex** | **0** | **0** | **0** | **2 (56 animals)** | **2** |
| - Mortality- Hemodynamics | -- | -- | -- | 2 (56 animals)2 (56 animals) | 22 |
| **Phosphodiesterase inhibitors** | **0** | **0** | **4** | **2 (39 animals)** | **6** |
| - Mortality- Hemodynamics- Other outcomes | --- | --- | 232 | 1 (8 animals)2 (39 animals)- | 352 |
| **Bay K 8644 and CGP 28932** | **0** | **0** | **0** | **3 (96 animals)** | **3** |
| - Mortality- Hemodynamics- Adverse effects | --- | --- | --- | 3 (96 animals)3 (96 animals)1 (40 animals) | 331 |
| **Digoxin** | **0** | **0** | **0** | **3 (30 animals)** | **3** |
| - Mortality- Hemodynamics | -- | -- | -- | 2 (22 animals)3 (30 animals) | 23 |
| **Cyclodextrin** | **0** | **0** | **0** | **2 (30 animals)** | **2** |
| - Mortality- Hemodynamics | -- | -- | -- | 2 (30 animals)2 (30 animals) | 22 |
| **Liposomes** | **0** | **0** | **0** | **2 (31 animals)** | **2** |
| - Hemodynamics- Other outcomes | -- | -- | -- | 2 (31 animals)1 (7 animals) | 21 |
| **Fructose-1,6-diphosphate** | **0** | **0** | **0** | **1 (60 animals)** | **1** |
| - Mortality- Hemodynamics | -- | -- | -- | 1 (60 animals)1 (60 animals) | 11 |
| **PK 11195** | **0** | **0** | **0** | **1 (12 animals)** | **1** |
| - Mortality- Hemodynamics | -- | -- | -- | 1 (12 animals)1 (12 animals) | 11 |
| **Triiodothyronine** | **0** | **0** | **0** | **1 (10 animals)** | **1** |
| - Mortality- Hemodynamics | -- | -- | -- | 1 (10 animals)1 (10 animals) | 11 |

No controlled trials were found. Some studies evaluated more than one outcome.

\*1 case report full text articlenot found (not included in appendix 3)

\*\*1 case report full text article not found (not included in appendix 3)

\*\*\*3 case reports full text article not found (not included in appendix 3)

**APPENDIX 6 (online) : Definitions**

First-line treatment: treatment initially provided to a symptomatic CCB-poisoned patient.

Patients refractory to first-line treatment: when desired effects (such as improvement in contractility, in heart rate, in blood pressure) were not reached with first-line treatments.

Rescue treatments: treatment provided to patients in refractory shock or peri-arrest.

Refractory shock: persistent cardiovascular failure associated with organ failure despite the administration of supportive care and other antidotal therapies.

Signs of CCB toxicity: hemodynamic abnormalities, such as low heart rate (<60 per minute in adults), low blood pressure (systolic <100 mmHg or mean arterial pressure <65 mmHg in adults), myocardial dysfunction or abnormal peripheral vascular resistances.

Myocardial dysfunction: decrease in myocardial contractility apparent on echocardiography or a documented cardiac index of less than 2.2 L/min/m2 (37).

Shock: state characterized by inadequate blood flow and oxygen delivery to organs and tissues (37).

Vasoplegic shock: state characterized by inadequate blood flow and oxygen delivery to organs and tissus in the context of decrease peripheral vascular resistances.

N.B.: We adopted reference values and definitions published by the American College of Cardiology (37), although members also recognized the importance of clinical judgement.

**APPENDIX 7 (online) : Rationale for not recommending or not suggesting some treatments**

- The workgroup recommends not to use methylene blue as a first-line treatment given experience is limited to a few case reports (95-98). (1D).

- The workgroup recommends not to use levosimendan, a calcium channel opening drug based on lack of efficacy in animal studies and unknown risks versus benefits in the clinical setting (99) (1D).

- The workgroup suggests not to use glucagon because case series reported variable effects (100-107). Vomiting and hyperglycemia (100,102-107) have been reported in several case reports, and more effective interventions for the treatment of CCB poisoning are available (2D).

- The workgroup recommends not to or suggests not to use the following treatments based on insufficient experience and scientific scrutiny: digoxin, liposomes, fructose 1,6 diphosphate, PK11195, BK8644, CPG28932, potassium antagonists, triidothyronine, cyclodextrin, sugamadex (24), amrinone or other PDE-inhibitors, L-carnitine (31), plasma exchange (96), CVVHDF (21), charcoal hemoperfusion (108), albumin dialysis, MARS (29), intra-aortic balloon pump (16). (1D-2D)