27e Congrès francophone
ACTUALITÉS EN RÉANIMATION
Médecine Intensive, Surveillance Continue
et Urgences Graves

Intoxications par cardiotropes : quelles nouveautés ?

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No COI

AER
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Intoxications par cardiotropes : généralités

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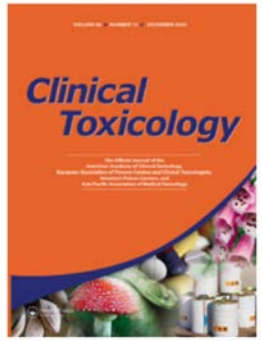
Cardiotropic "drugs" in toxicology and in ICU

A larger entity than cardiovascular xenobiotics

- Rural toxicants : organophosphates, pesticides …
- Industrial toxicants: cyanide …
- Household toxicants: CO, trichloroethylene …
- Plants : digitalis, aconit, colchicine …
- Over-the-counter: « Best life » (sibutramine)

- Drugs (cardiac and/or vascular toxicity):
  - Beta-blockers (class 2)
  - Calcium-channel antagonists (class 4)
  - Sodium-channel blockers = membrane stabilising agents (class 1)
  - Potassium channel blockers : cordarone, sotalol (class 3)
  - Cardioglycosides : digitalis (class 5)

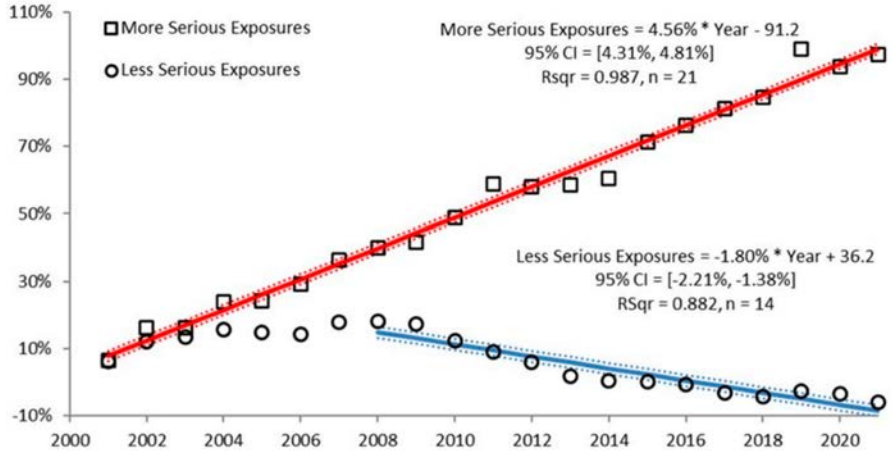


Poisonings with cardiotoxicants

Gummins DD et al. Clin Tox 2022
Gummins DD et al. Clin Tox 2020
Mowri et al. Clin Tox 2016

2021 Annual Report of the National Poison Data System© (NPDS) from America's Poison Centers: 39th Annual Report

Human exposures with less serious outcomes have decreased since 2008 but those with more serious outcomes have increased 4.56% / year since 2000



ATD polycycliques : 3ème cause d'intoxication chez l'adulte (7.1%, vs analgésiques = N°1, 11.1%) et 2ème de DC.

Agents cardiovasculaires : 4ème cause d'intoxication adulte (6.8%) et 2 à 4ème cause de DC selon les reports (N°1 : paracetamol 8.9%) ; I. Calciques 5% (N°6), beta-bloquants 3.6% (N°7)

Un choc sur une intoxication est un facteur de surmortalité

Lariboisiere ICU (sur 10 ans)	N= 3672	Mortalité
Nombre total d'intoxications	100 %	4 %
Etat de choc	11 %	31 %

Une intoxication par cardiotropes est un facteur de surmortalité

Décès = 10% si intoxication par cardiotropes
(choc sur cardiotrope = 24%)

Classification de Vaughan-Williams des anti-arythmiques

Antiarrhythmic Drugs are divided into five groups:

Class I: **Na^+ channel blockers** (e.g. Quinidine)

Class II: **β-Blockers** (e.g. Propanolol)

Class III: **I_{Kr} channel blockers** (e.g. Sotalol) Cordarone, Brétylium

Class IV: **L-type Ca^{2+} channel blockers** (e.g. Verapamil)

Class V: **Miscellaneous** including adenosine, K^+ and Mg^{2+} ions
Digitaliques

Vaughan-Williams EM. J Clin Pharmacol 1984, 24:129.

Subdivision de la classe I des anti-arythmiques

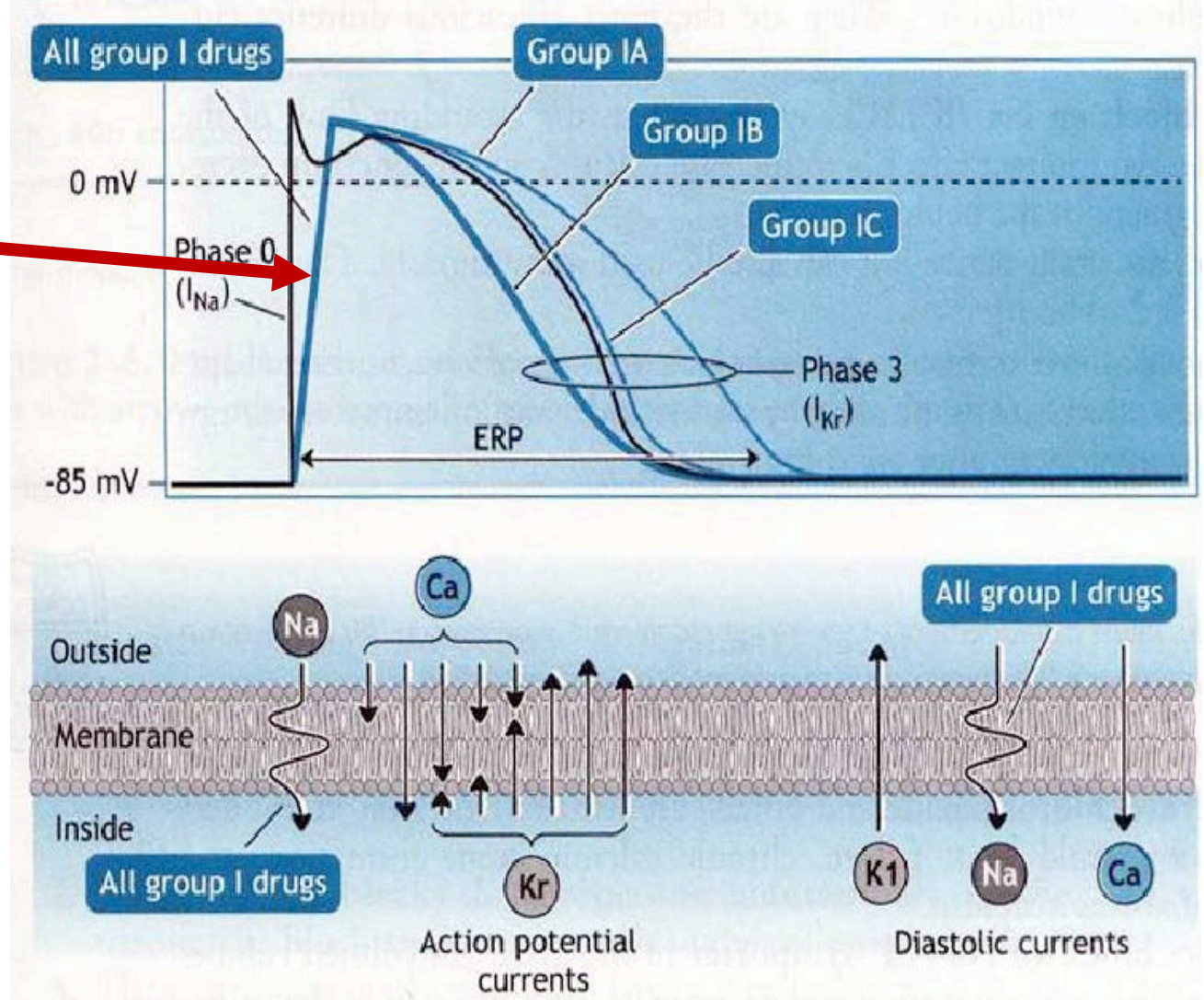


Figure 3–5. The effects of class I antiarrhythmic agents. Class IA drugs prolong the action potential, class IB drugs shorten the action potential, and class IC drugs have no effect on the action potential.

Classe I : Dépression du courant sodique rapide

IA - Cinétique intermédiaire + dépression du courant potassique

- Quinidine
- Procainamide
- Disopyramide
- Ajmaline

I B - Cinétique rapide

- Lidocaine
- Mexilétine
- Diphénylhydantoine
- Tocainide

IC - Cinétique lente

- Flécainide
- Encainide
- Propafénone
- Lorcainide

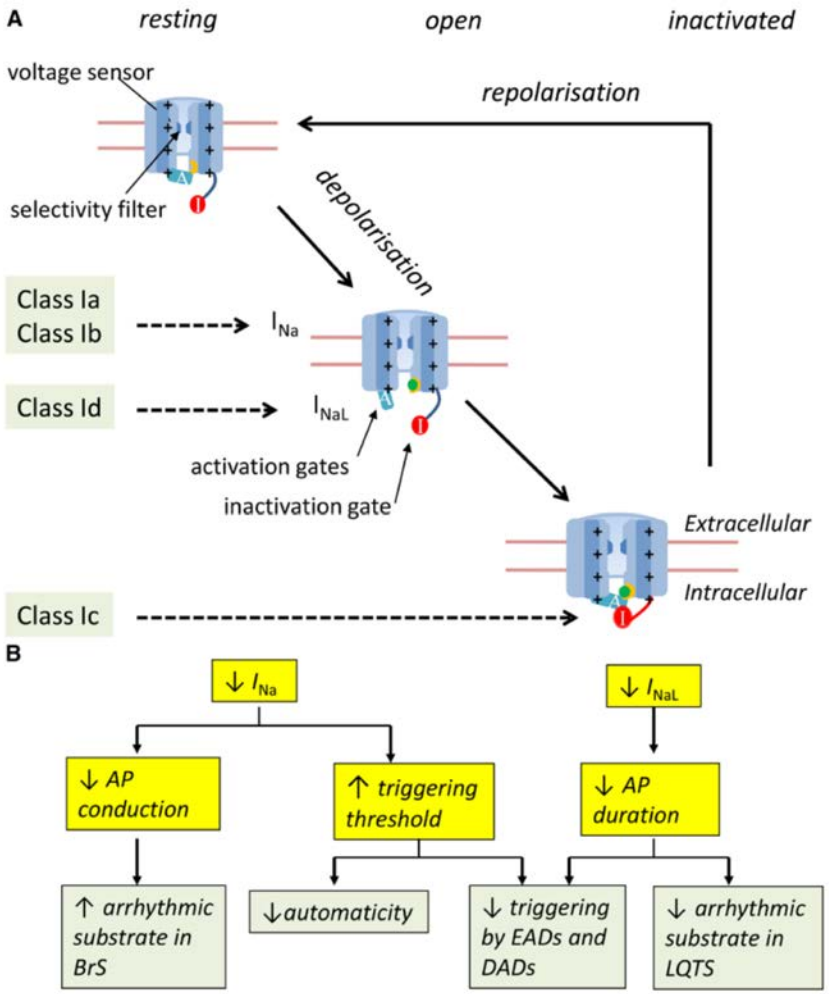
Circulation

SYSTEMATIC REVIEW

Modernized Classification of Cardiac Antiarrhythmic Drugs

Lei et al,
Circulation 2018

Ming Lei, BM, MSc, DPhil
Lin Wu, BM, MSc, MD
Derek A. Terrar, BSc, MA, PhD
Christopher L.-H. Huang, MA, BMBCh, DM, DSc, PhD, MD, ScD



existence of Na^+ current components (for Class I), advances in autonomic (often G protein–mediated) signaling (for Class II), K^+ channel subspecies (for Class III), and novel molecular targets related to Ca^{2+} homeostasis (for Class IV). We introduce new classes based on additional targets, including channels involved in automaticity, mechanically sensitive ion channels, connexins controlling electrotonic cell coupling, and molecules underlying longer-term signaling processes affecting structural remodeling.

Classe 0 : HCN channel blockers (ivabradine)
Classe I : Voltage-gated Na+ channel blockers ; Ia, Ib, Ic, Id
Classe II : Autonomic inhibitors and activators (récepteurs béta, muscariniques, adenosine) ; Iia à IIe
Classe III : K+ channel blockers and openers ; IIIa, IIIb, IIIc
Classe IV : Ca2+ handling modulators ; IVa à IVe
Classe V : Mechanosensitive channel blockers
Classe VI : Gap junction channel blockers
Classe VII : Upstream target modulators

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Intoxications par cardiotropes : par classe de cardiotoxiques

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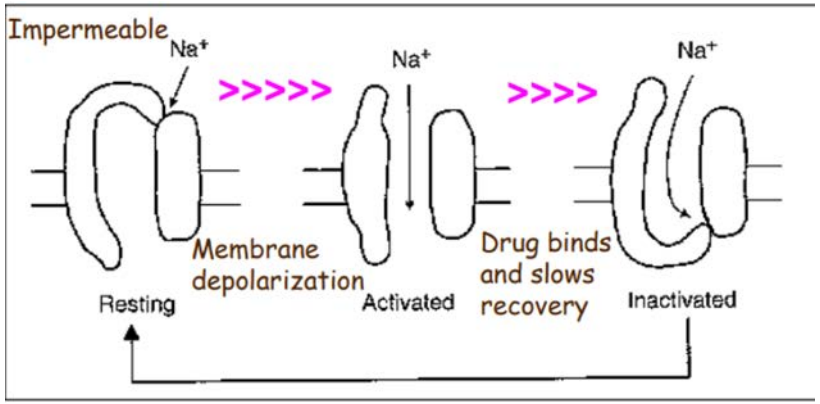
No COI

1 Poisonings with sodium channel blockers (SCB)
Molecules ayant à doses toxiques un ESM

- **Anti-arythmiques (classe 1) :** quinidine, lidocaine, phénytoïne, méxilétine, cibenzoline, tocaïnide, procaïnamide, disopyramide, flécaïnide, propafénone
- **Certains β-bloquants (classe 2)** : propranolol, acébutolol, nadoxolol, pindolol, penbutolol, labétalol, oxprénolol
- **Antidépresseurs polycycliques** : amitritptyline, imipramine, clomipramine, maprotiline
- **Inhibiteurs du recaptage de la sérotonine** : citalopram, venlafaxine
- **Anti-épileptiques :** carbamazépine, phénytoïne
- **Certaines phénothiazines** : thioridazine+++, hydroxyzine (doses extrêmes)
- **Antalgiques** : dextropropoxyphène (retiré du marché)
- **Anti-paludéens** : chloroquine, quinine
- **Cocaïne**
- **Lithium** (doses extrêmes)

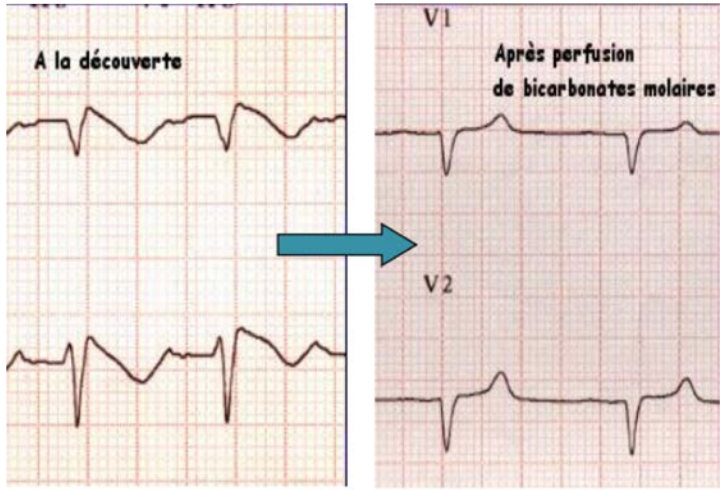


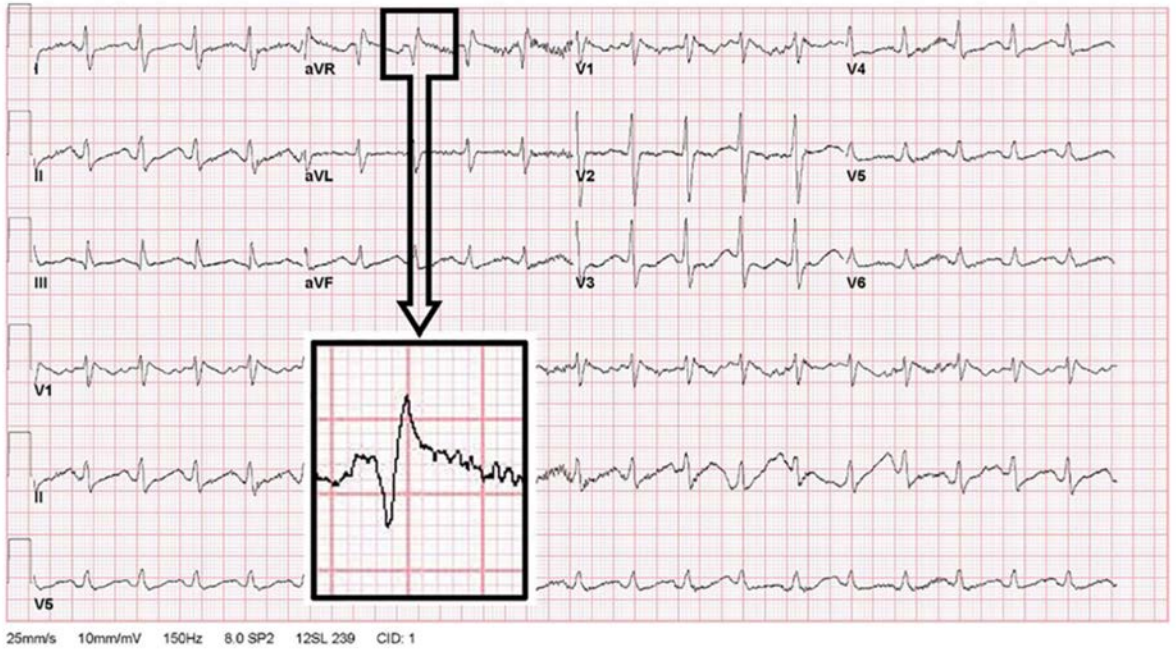
Lavonas et al, Circulation 2023

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

American Heart Association.

Carbamazepine
Chloroquine*
Cocaine†
Diphenhydramine (nautamine, actifed)
Flecainide
Hydroxychloroquine*
Lamotrigine (lamictal)
Lacosamide (vimpat)
Propafenone
Quinine
Quinidine
Thioridazine
Taxus spp. (yew)
Topiramate (epitomax)
TCAs‡
Venlafaxine
Zonisamide (AE : zonegran)





REVIEW Open Access

Management of pharmaceutical and recreational drug poisoning

Mégarbane et al AIC 2020

Experts from SRLF, SFMU, STC, SFTA, GFRUP

Field 8: Specificities of cardiotoxicant poisoning

STRONG RECOMMENDATION/GRADE 1+/ STRONG CONSENSUS

R 8.1.2: Fluid resuscitation should be performed as first-line procedure in the presence of toxin-induced hypotension.

STRONG RECOMMENDATION/GRADE 1+/ STRONG CONSENSUS

R 8.1.3: A catecholamine should be administered if fluid resuscitation has failed in the presence of toxin-induced shock.

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.1.4: In patients with toxin-induced shock, in the absence of haemodynamic assessment, the experts suggest first-line treatment with norepinephrine or epinephrine depending on the clinical presentation and the toxin involved.

Recommendations according to the GRADE methodology		
High level of evidence	Strong recommendation "the intervention must be used"	Grade 1+
Moderate level of evidence	Optional recommendation "the intervention should probably be used"	Grade 2+
Low level of evidence	Recommendation in the form of an expert opinion "The experts suggest..."	Expert opinion
Moderate level of evidence	Optional recommendation "the intervention should probably not be used"	Grade 2–
High level of evidence	Strong recommendation "the intervention must not be used"	Grade 1–
Low level of evidence		No recommendation

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.3: The experts suggest that extracorporeal life support using veno-arterial (VA) ECMO should be implemented to improve survival in patients with cardiotoxicant poisoning, in refractory cardiac arrest or cardiovascular failure refractory to pharmacological treatment.

Treatment for sodium channel blockers poisoning

- Antidote – sodium as bicarbonate 8.4% or other concentrated form (750 ml, 1mmol/ml) : if MAP < 65 mmHg and QRS > 120 ms

Antidote	Indication	Initial Dose (Adult)*	Initial Dose (Pediatric)*	Maintenance Infusion	Notes
Sodium bicarbonate†	Sodium channel blockers Cocaine	50–150 mEq	1–3 mEq/kg	Prepare 150 mEq/L solution, infuse at 1–3 $mL \cdot kg^{-1} \cdot h^{-1}$	Watch for hypernatremia, alkalemia, hypokalemia, hypochloremia.

- Symptomatic : vasopressors, intubation
- Diazepam if chloroquine
- No other antiarrythmic treatment proven
- Empirical indication ECLS if > 3mg/h (0.5µg/kg/min) epinephrine and not improving

Lavonas et al, Circulation 2023

American Heart Association.

Recommendations for the Treatment of Patients With Life-Threatening Sodium Channel Blocker Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend using sodium bicarbonate to treat life-threatening cardiotoxicity from tricyclic and/or tetracyclic antidepressant poisoning.
2a	C-LD	2. It is reasonable to use sodium bicarbonate to treat life-threatening cardiotoxicity caused by poisoning from sodium channel blockers other than tricyclic or tetracyclic antidepressants.
2a	C-LD	3. It is reasonable to use extracorporeal life support, such as VA-ECMO, to treat refractory cardiogenic shock from sodium channel blocker poisoning.
2b	C-LD	4. It may be reasonable to use Vaughan-Williams class Ib antidysrhythmics (eg, lidocaine) to treat life-threatening cardiotoxicity from class Ia or Ic sodium channel blockers.
2b	C-LD	5. It may be reasonable to use intravenous lipid emulsion to treat life-threatening sodium channel blocker poisoning refractory to other treatment modalities.

CLASS 1 (STRONG) Benefit >>> Risk

CLASS 2a (MODERATE) Benefit >> Risk

CLASS 2b (WEAK) Benefit ≥ Risk

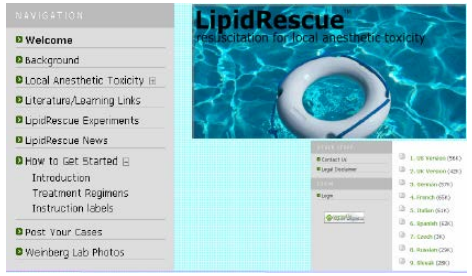
LEVEL B-NR (Nonrandomized)

LEVEL C-LD (Limited Data)

Lipid emulsion to treat cardiotoxicant drug-related toxicity

2

Fat emulsion for local anesthetic toxicity (Medialipid™, Intralipid™)



To treat severe anesthetics side-effects in the OR as well as membrane-stabilizing agent or calcium-channel blocker poisonings.

Dose regimen: 1.5 ml/kg IV bolus then 0.25 ml/kg/min infusion

Mechanisms:

- Lipid sink / sponge: alteration of tissue distribution
- Modulator of myocardial energy, overcoming the inhibition of fatty acid-dependent metabolism
- Activator of myocardial Ca^{2+} channel increasing Ca^{2+} current

→ Cardiotonic activity

- Other toxin-specific mechanisms?
- Vaso-active and cytoprotective properties?

Better decrease in serum concentrations for lipophilic cardiotoxins with high partition constant and distribution volume

Sirianni AJ. Ann Emerg Med 2008
Finn SD. Anesthesia 2009
Weinberg GL. Anesthesiology 2009
Dean P. Anesthesia 2010

Review

Lipid Emulsion to Treat Acute Poisonings: Mechanisms of Action, Indications, and Controversies

pharmaceutics

2023

Karim Jaffal [1,2], Lucie Chevillard [1,2] and Bruno Mégarbane [1,2,*]

Present evidence supports the use of ILE as first-line therapy to reverse local anesthetic-related systemic toxicity and as adjunct therapy in lipophilic non-local anesthetic drug overdoses refractory to well-established antidotes and supportive care. However, the level of evidence is low to very low, as for most other commonly used antidotes.

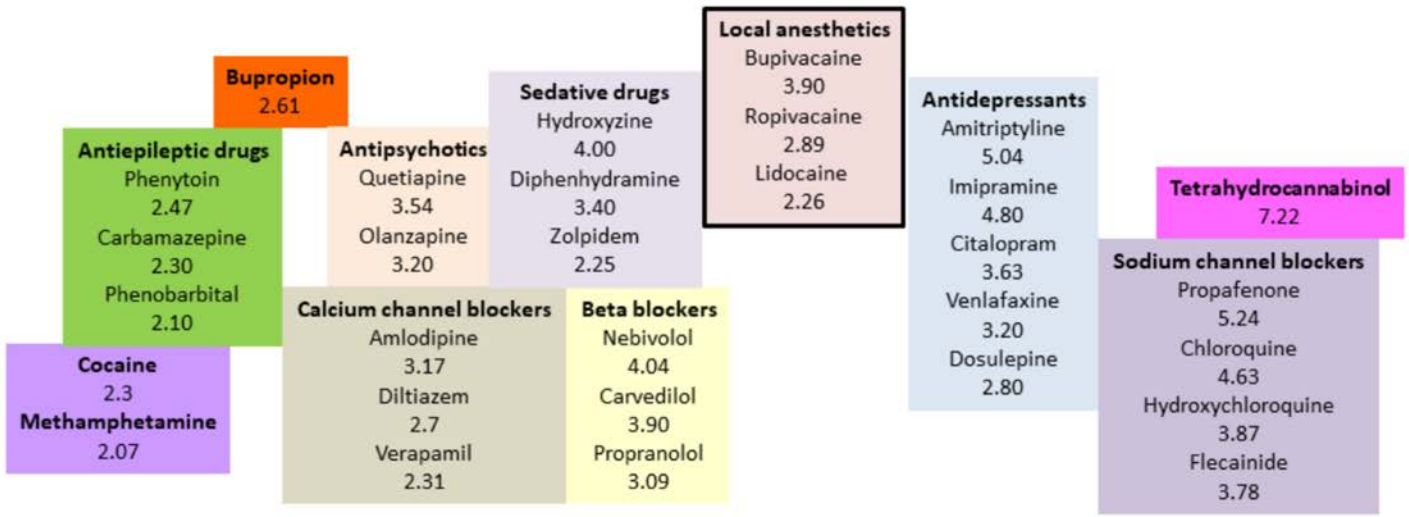


Figure 2. Partition coefficients of some selected lipophilic drugs for which the use of lipid emulsion could be considered in poisoning.

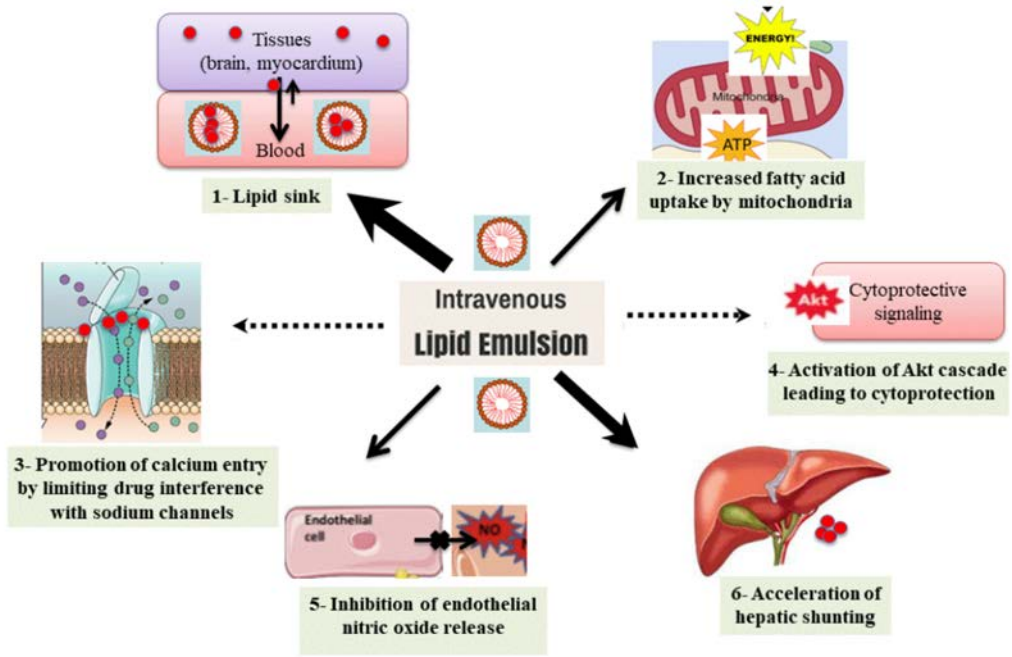


Figure 3. Suggested mechanisms for lipid resuscitation (adapted from Weinberg GL [6]).

Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning

For the management of cardiac arrest:
We recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins.

For the management of life-threatening toxicity:
- We suggest using ILE as a part of treatment in bupivacaine toxicity and we recommend its use if other therapies fail;
- We suggest using ILE if other therapies fail for toxicity due to other local anesthetics, amitriptyline, and bupropion;
- Our recommendations are neutral for all other toxins.

In the treatment of non-life-threatening toxicity, recommendations varied according to the balance of expected risk/benefit for each toxin

Gosselin S. *Clin Tox* 2016

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.2.1: The experts suggest that ILE should not be administered to patients with cardiotoxicant poisoning in the absence of signs of clinical severity or poor prognosis.

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.2.2: The experts suggest that ILE should be administered to patients with local anaesthetic poisoning with signs of severity in addition to resuscitation measures.

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.2.3 The experts suggest that ILE should not be administered in the case of poisoning with non-fat-soluble cardiotoxicants.

OPTIONAL RECOMMENDATION/GRADE 2+/ STRONG CONSENSUS

R 8.2.4: ILE should probably be administered, after failure of standard resuscitation measures, in the case of immediately life-threatening fat-soluble cardiotoxicant poisoning prior to ECMO.

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.2.5: The experts suggest that ILE should not be administered to prevent possible deterioration.

Mégarbane et al. AIC 2020.
SRLF, SFMU, STC, SFTA, GFRUP

Lavonas et al, Circulation 2023

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

American Heart Association.

Recommendations for the Management of Patients With Life-Threatening Local Anesthetic Poisoning

COR	LOE	Recommendations
1	C-LD	1. We recommend the administration of intravenous lipid emulsion for local anesthetic poisoning.
1	C-LD	2. We recommend the use of benzodiazepines to treat seizures associated with local anesthetic systemic toxicity.
2a	C-LD	3. It is reasonable to administer sodium bicarbonate for life-threatening wide-complex tachycardia associated with local anesthetic toxicity.
2a	C-EO	4. It is reasonable to administer atropine for life-threatening bradycardia associated with local anesthetic systemic toxicity.
2a	C-EO	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO in local anesthetic toxicity with refractory cardiogenic shock.

CLASS 1 (STRONG) Benefit >>> Risk

CLASS 2a (MODERATE) Benefit >> Risk

LEVEL C-LD (Limited Data)

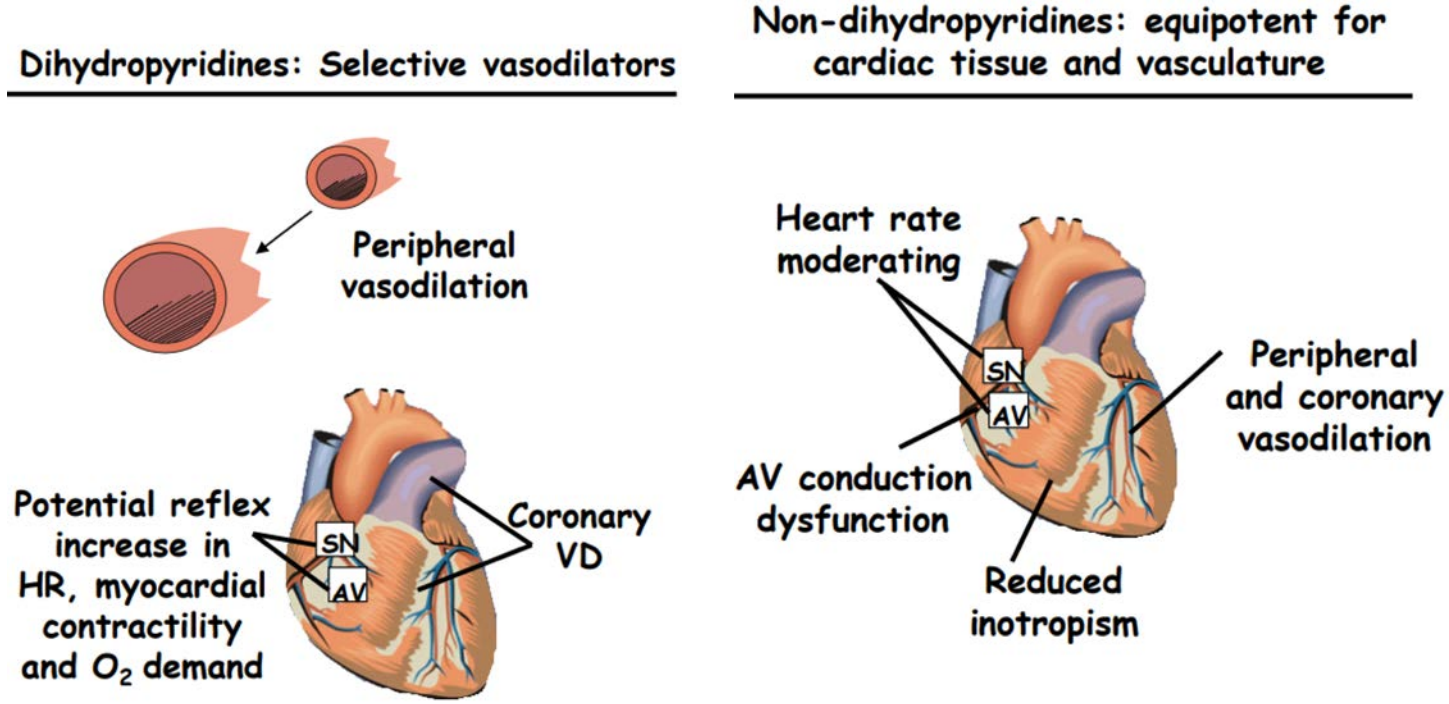
LEVEL C-EO (Expert Opinion)

3 Calcium-channel antagonist poisonings

Five different CCB classes:

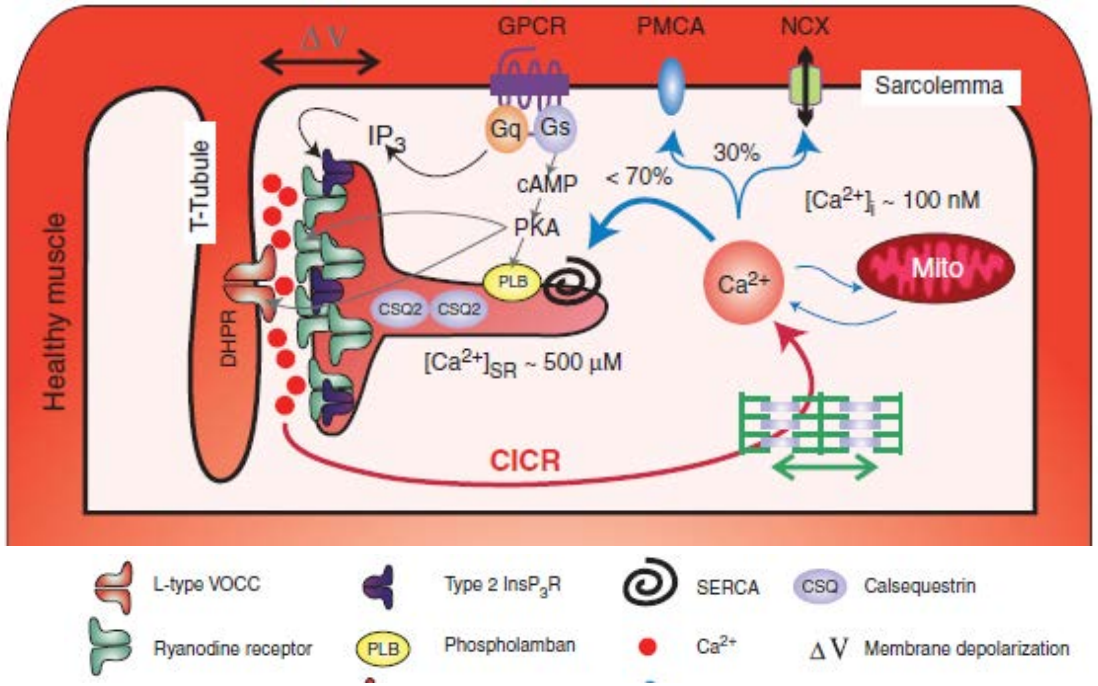
- ✓ Dihydropyridines (nifedipine and amlodipine)
- ✓ Phenylalkylamine (verapamil)
- ✓ Benzothiazepine (diltiazem)
- ✓ Diphenylpiperazine (mibefradil)
- ✓ Diarylaminopropylamine (bepridil).

Harris NS. *N Eng J Med* 2006

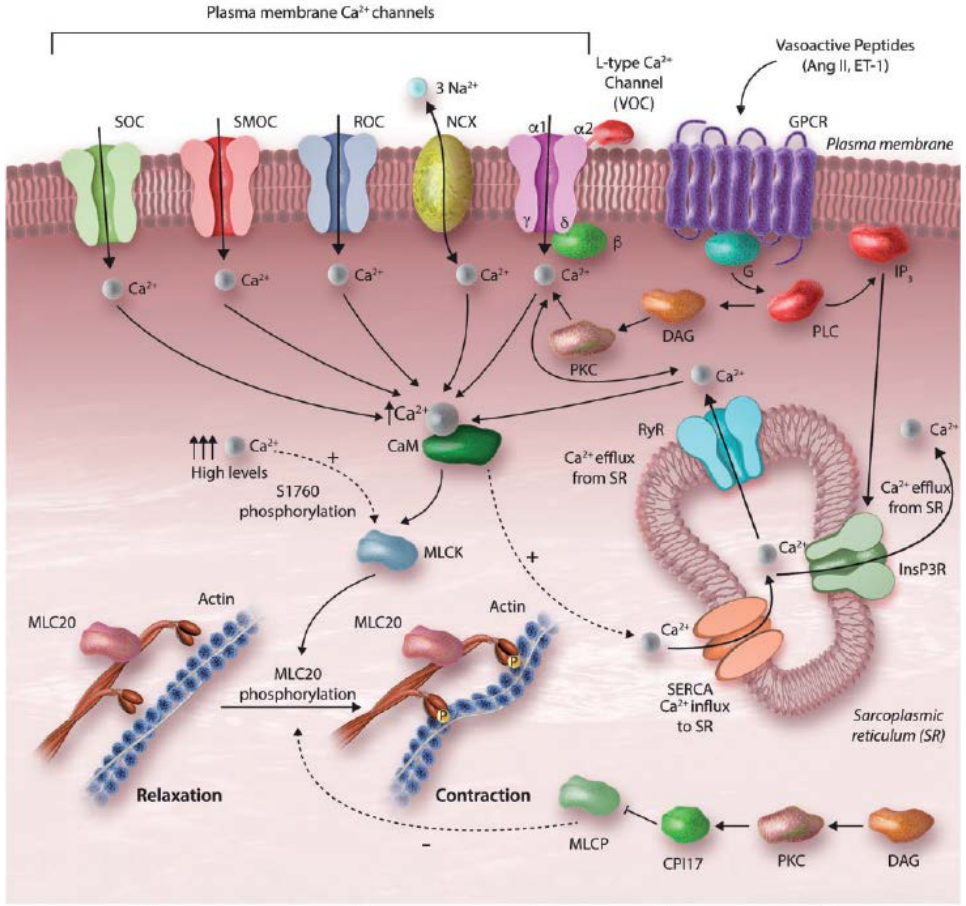


Biological Predictive value of severity : hyperglycemia, drugs concentrations (verapamil)

Intracellular calcium: positive inotropic effect, positive effect on mean arterial pressure, heart rate and conduction abnormalities



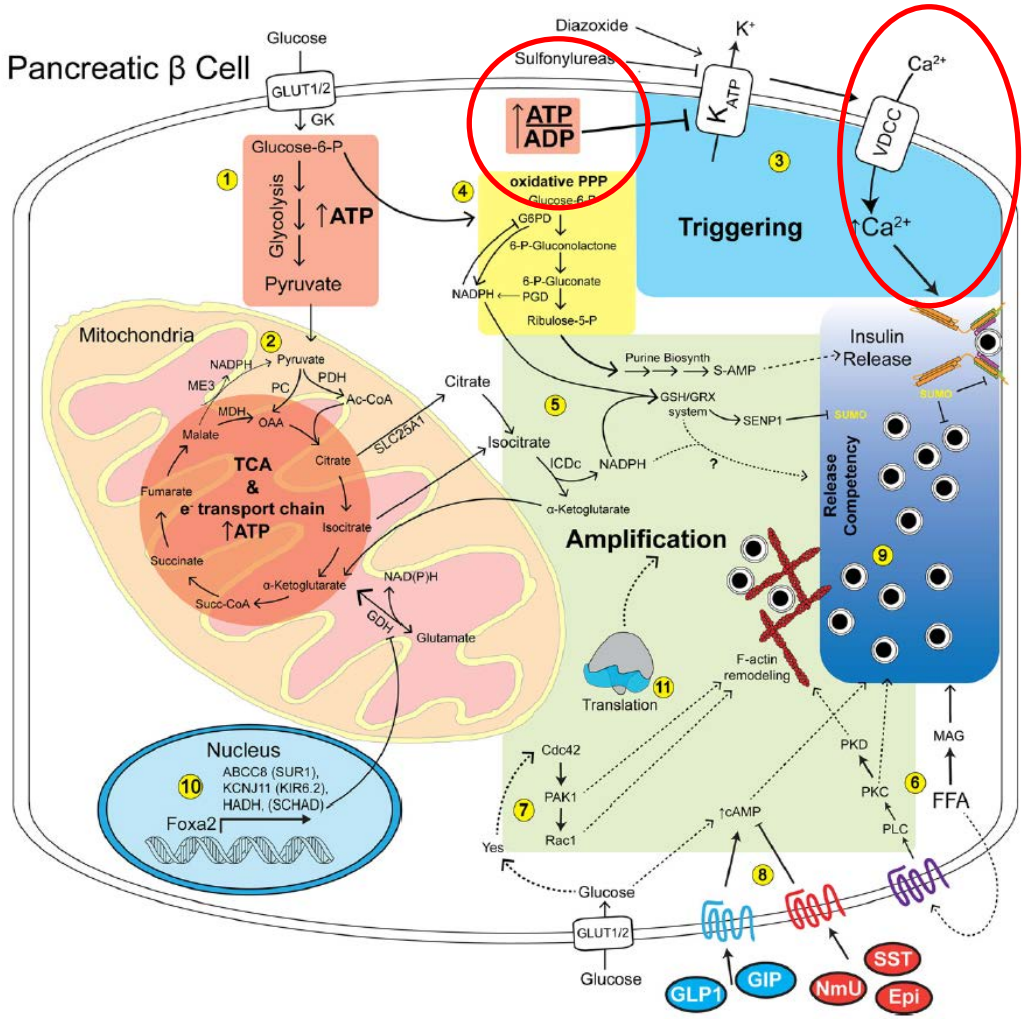
Touyz et al. Cardiovasc Res 2007



High doses of calcium gluconate appeared to be more effective than lower doses. **Monitoring**: ionized calcium < 1.5-2 upper limit

Calcium chloride	CCBs	2000 mg 28 mEq Ca^{2+} 20 mL 100 mg/mL solution	20 mg/kg 0.28 mEq Ca^{2+}/kg 0.2 mL/kg 100 mg/mL solution	20–40 $mg \cdot kg^{-1} \cdot h^{-1}$ 0.28–0.56 mEq $Ca^{2+} \cdot kg^{-1} \cdot h^{-1}$ 0.2–0.4 $mL \cdot kg^{-1} \cdot h^{-1}$ 100 mg/mL solution	Titrate to blood pressure. Do not exceed serum ionized calcium concentration 1.5–2 times the upper limits of normal. Administer through central line, especially in children.
Calcium gluconate	CCBs	6000 mg 28 mEq Ca^{2+} 60 mL 100 mg/mL solution	60 mg/kg 0.28 mEq/kg Ca^{2+} 0.6 mL/kg 100 mg/mL solution	60–120 $mg \cdot kg^{-1} \cdot h^{-1}$ 0.28–0.56 mEq $Ca^{2+} \cdot kg^{-1} \cdot h^{-1}$ 0.6–1.2 $mL \cdot kg^{-1} \cdot h^{-1}$ 100 mg/mL solution	Titrate to blood pressure. Do not exceed serum ionized calcium concentration 1.5–2 times the upper limits of normal.

Insuline



Calwat et Cobb, Pharmaco Ther, 2017. Mechanisms of the amplifying pathway of insulin secretion in the β cell

Bartlet, Crit Care Nurse 2016

Mechanisms of Action of High-Dose Insulin/Glucose Therapy

The common opinion is that high-dose insulin/glucose therapy works by 3 mechanisms of action to reverse cardiotoxic poisoning.[2]

1. Positive inotropy: The positive inotropic effects of insulin have been demonstrated in many animal experiments.[11-17] These effects may be due to the effect of insulin on glucose metabolism and/or to a separate mechanism.

2. Vasodilatation: Insulin dilates peripheral vessels.[18,19]

3. Metabolic effects: Calcium channel blocker poisoning inhibits the L-type voltage-sensitive ion channels in the pancreas, decreasing insulin release.[14,20,21] Insulin

Better outcomes are reported using insulin with lower rates of vasoconstrictive complications than vasopressor-only therapy.

Bolus 1 UI/kg followed by 1-10 UI/kg/h

Monitoring: Protocolized care reduces the risk of hypoglycemia. Hypokalemia and volume overload.

Curr Hypertens Rep (2012) 14:293–303
DOI 10.1007/s11906-012-0269-4

Pleiotropic Effects of Calcium Channel Blockers

R. Preston Mason

- Some dihydropyridines :
- Antioxydants
- Increase endothelial NO synthase and its ARNm
- At toxic concentrations, participation of NO may be important

Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose

BMJ case reports, 2012

Nidhi Aggarwal, Yizhak Kupfer, Chanaka Seneviratne, Sidney Tessler

Antidote	Indication	Initial Dose (Adult)*	Initial Dose (Pediatric)*	Maintenance Infusion	Notes
Methylene blue	CCBs Methemoglobinemia	1–2 mg/kg, repeated every hour if needed	Same as adult	1 $mg \cdot kg^{-1} \cdot h^{-1}$ (for vasodilatory shock)	Maximum 5–7 mg/kg

Lavonas et al, Circulation 2023

American Heart Association.

Recommendations for the Management of Patients With Life-Threatening Calcium Channel Blocker Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend administering vasopressors for hypotension from calcium channel blocker (CCB) poisoning.
1	B-NR	2. We recommend administering high-dose insulin for hypotension due to CCB poisoning.
2a	C-LD	3. It is reasonable to administer calcium for CCB poisoning.
2a	C-LD	4. It is reasonable to administer atropine for hemodynamically significant bradycardia from CCB poisoning.
2a	C-LD	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for cardiogenic shock due to CCB poisoning that is refractory to pharmacological interventions.
2b	C-LD	6. It might be reasonable to attempt electrical pacing for CCB poisoning with refractory bradycardia.
2b	C-LD	7. The usefulness of a glucagon bolus and infusion for CCB poisoning is uncertain.
2b	C-LD	8. The usefulness of administering methylene blue for refractory vasodilatory shock due to CCB poisoning is uncertain.
3: No Benefit	C-LD	9. The routine use of intravenous lipid emulsion (ILE) therapy for CCB poisoning is not recommended.

CLASS 1 (STRONG) Benefit >>> Risk

LEVEL B-NR (Nonrandomized)

CLASS 2a (MODERATE) Benefit >> Risk

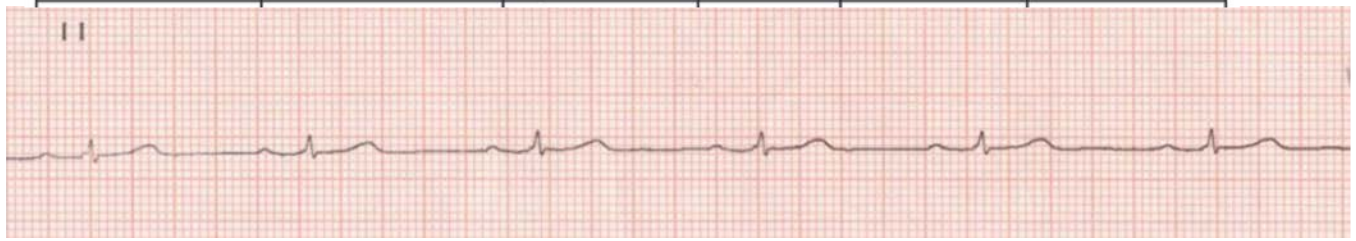
LEVEL C-LD (Limited Data)

CLASS 2b (WEAK) Benefit ≥ Risk

Class 3: Harm (STRONG) Risk > Benefit

4 Beta-blocker poisonings treatment

Antidote	Indication	Initial Dose (Adult)*	Initial Dose (Pediatric)*	Maintenance Infusion	Notes
Atropine	β-Blockers CCBs Digoxin Local anesthetics	0.5–1.0 mg every 3–5 min up to 3 mg	0.02 mg/kg	None	

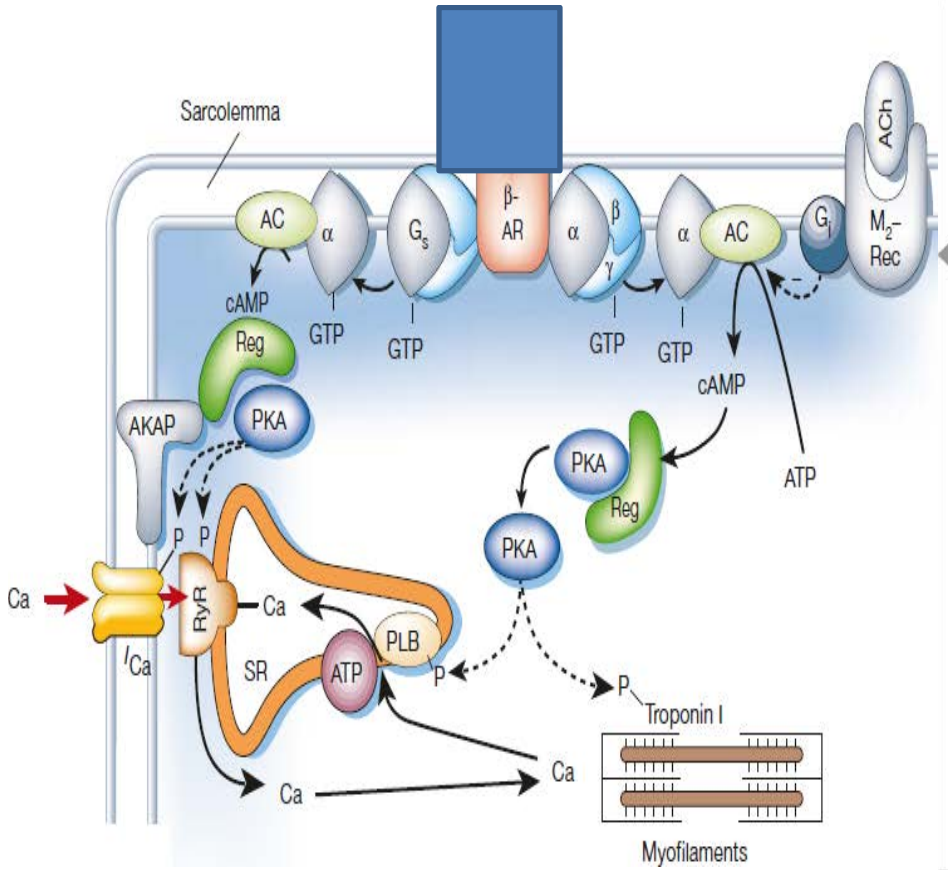


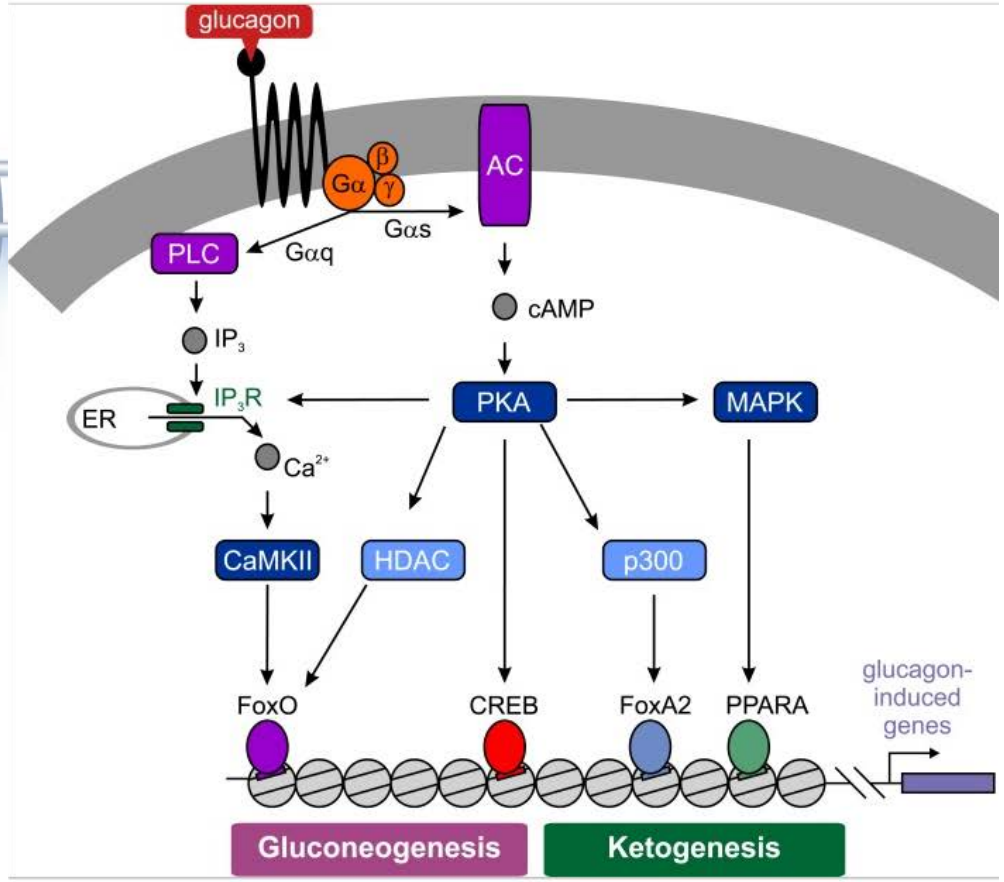
- Atropine
- Glucagon
- Dobutamine
- Isoprenaline – specific antidote beta receptor
- Dialysis (atenolol, sotalol or bisoprolol if terminal renal failure)
- Repeated activated charcoal (severe poisoning, PL)
- Insulin-euglycemia
- Lipid emulsion?
- ECMO

According to severity and prognosis (value of blood lactate on admission)
Depending of presence of MSA (excess of mortality): other treatments

Glucagon - transduction of beta1 signal

propranolol

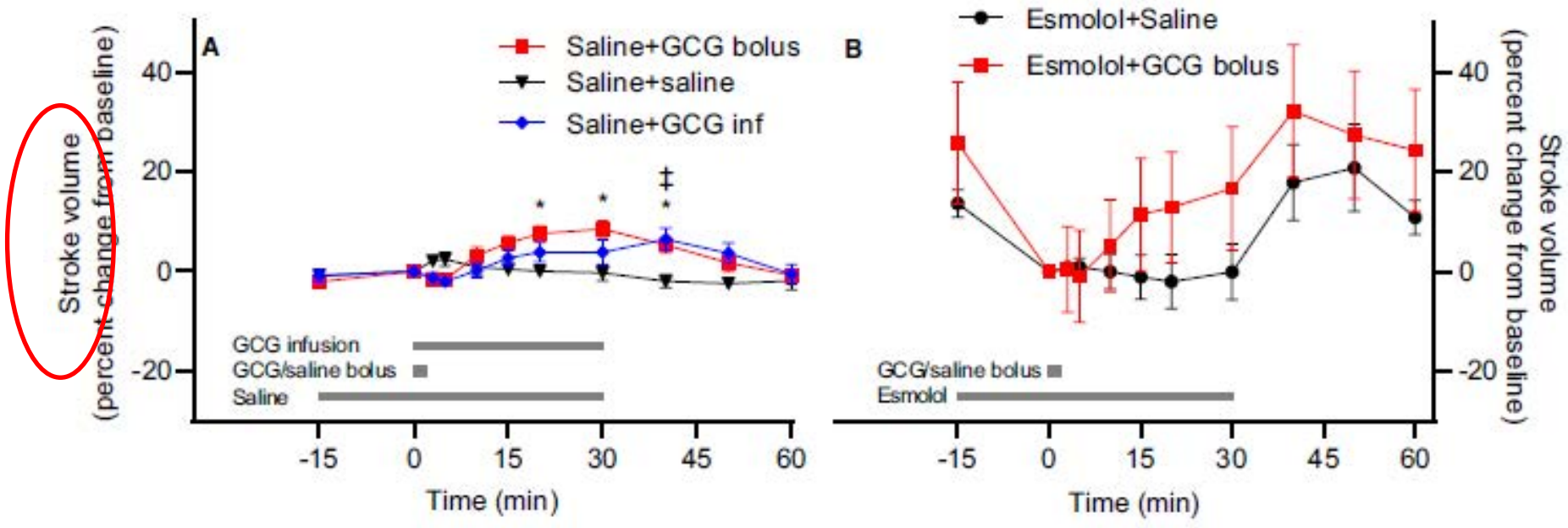




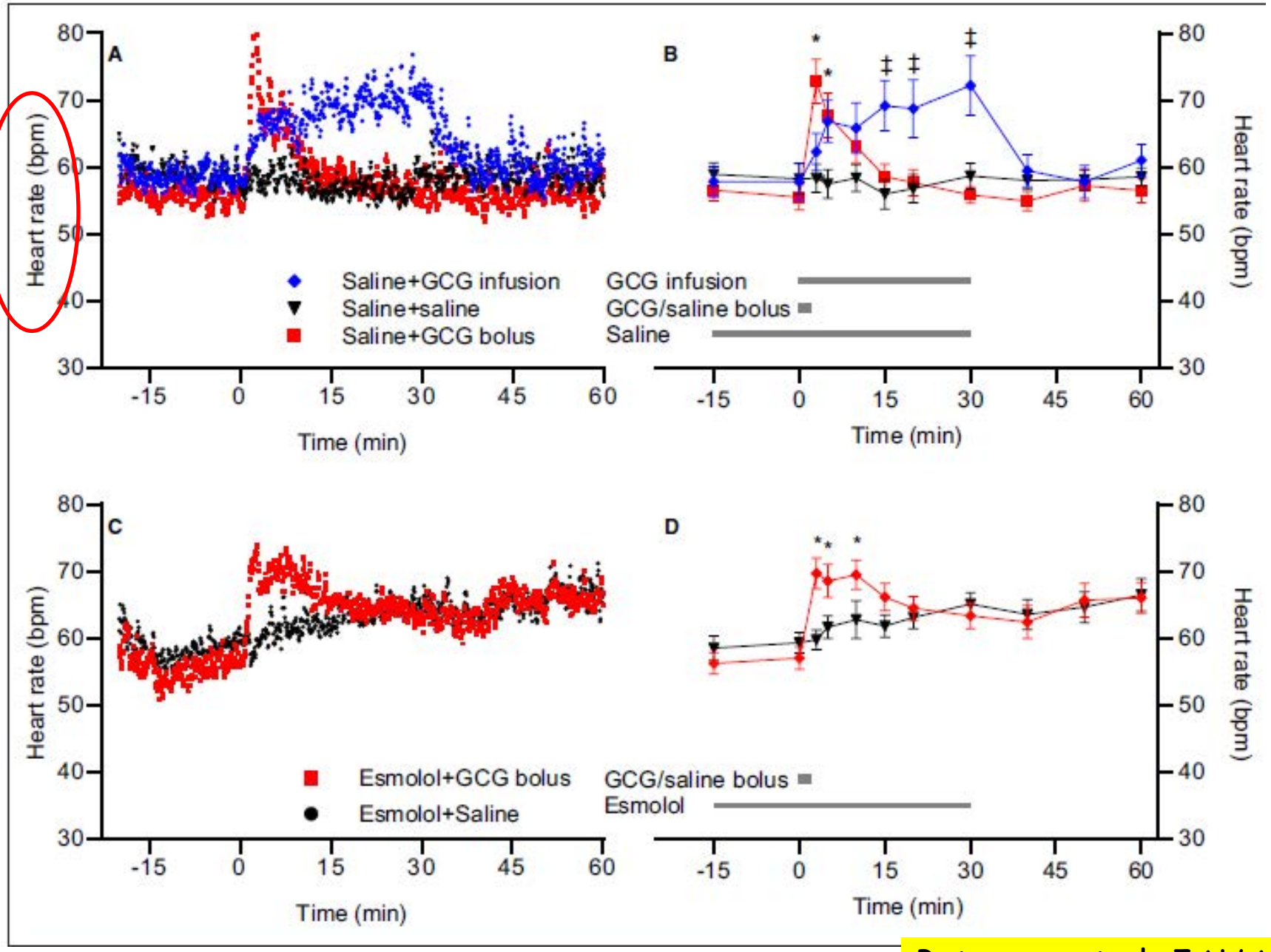
Antidote	Indication	Initial Dose (Adult)*	Initial Dose (Pediatric)*	Maintenance Infusion	Notes
Glucagon	β-Blockers CCBs	2–10 mg	0.05–0.15 mg/kg	1–15 mg/h (adult)	Anticipate vomiting.

High-Dose Glucagon Has Hemodynamic Effects Regardless of Cardiac Beta-Adrenoceptor Blockade: A Randomized Clinical Trial

- 10 healthy subjects, glucagon vs placebo
- Glucagon 50 µg/kg IVL over 2 min or continuous IV over 30 min



Petersen et al, JAHA 2020



Petersen et al, JAHA 2020

Dialysis for BB clearance – Extrip 2021 (systematic review & recommendations)

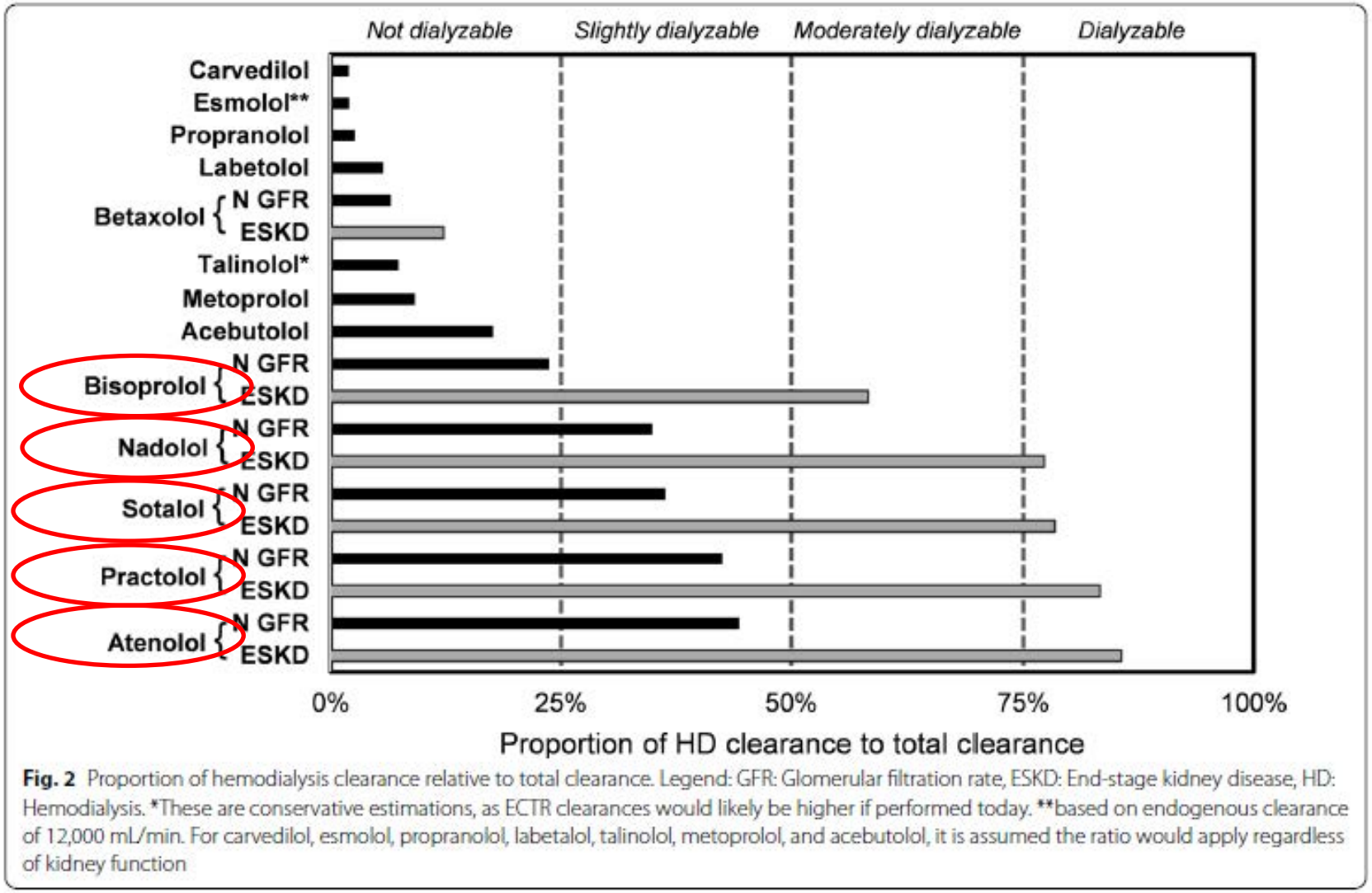


Fig. 2 Proportion of hemodialysis clearance relative to total clearance. Legend: GFR: Glomerular filtration rate, ESKD: End-stage kidney disease, HD: Hemodialysis. *These are conservative estimations, as ECTR clearances would likely be higher if performed today. **based on endogenous clearance of 12,000 mL/min. For carvedilol, esmolol, propranolol, labetalol, talinolol, metoprolol, and acebutolol, it is assumed the ratio would apply regardless of kidney function

Hemodialysis (not continuous VV techniques) as long as persistent shock

Bouchard et al, Crit Care, 2021

Lavonas et al, Circulation 2023

Recommendations for the Management of Patients With Life-Threatening Beta Blocker Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend that high-dose insulin be administered for hypotension due to β-blocker poisoning refractory to or in conjunction with vasopressor therapy.
1	C-LD	2. We recommend that vasopressors be administered for hypotension due to β-blocker poisoning.
2a	C-LD	3. It is reasonable to use a bolus of glucagon, followed by a continuous infusion, for bradycardia or hypotension due to β-blocker poisoning.
2a	C-LD	4. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for life-threatening β-blocker poisoning with cardiogenic shock refractory to pharmacological interventions.
2b	C-LD	5. It may be reasonable to administer atropine for β-blocker–induced bradycardia.
2b	C-LD	6. It may be reasonable to attempt electrical pacing for β-blocker–induced bradycardia.
2b	C-LD	7. It may be reasonable to use hemodialysis for life-threatening atenolol or sotalol poisoning.
3: No Benefit	C-LD	8. Intravenous lipid emulsion therapy is not likely to be beneficial for life-threatening β-blocker poisoning.

CLASS 1 (STRONG) Benefit >>> Risk

CLASS 2a (MODERATE) Benefit >> Risk

CLASS 2b (WEAK) Benefit ≥ Risk

Class 3: Harm (STRONG) Risk > Benefit

LEVEL B-NR (Nonrandomized)

LEVEL C-LD (Limited Data)

American Heart Association.

5 Cardioglycoside poisonings digitalis poisoning

Na/K - ATPase blockade
Circumstances: therapeutic overdose > suicide

Blood pressure is usually preserved (sympathic tone), while cardiac dysfunction possible

Cardiac arrhythmias may take almost any form and are responsible for mortality

Main prognostic factors:
male, aged, with AVB/arrythmia and hyperkaliemia

Digoxin immune Fab	Digoxin	Acute overdose: 1 vial for every 0.5 mg digoxin ingested Chronic poisoning: Use formula: dose in vials=serum digoxin concentration (ng/mL)×weight (kg)/100 Acute overdose, critically ill, ingested dose unknown: 10–20 vials	Same as adult	None	1 vial contains 40 mg Fab. Lower doses may be equally effective.[8]
Digoxin immune Fab	Yellow oleander *Bufo* toad venom	1200 mg (30 vials)	Unknown	None	

Lavonas et al, Circulation 2023

American Heart Association.

Recommendations for the Management of Patients With Life-Threatening Poisoning From Digoxin and Related Cardiac Glycosides

COR	LOE	Recommendations
1	B-NR	1. We recommend administration of digoxin-specific antibody fragments (digoxin-Fab) for digoxin or digitoxin poisoning.
2a	C-LD	2. It is reasonable to administer digoxin-Fab for poisoning due to *Bufo* toad venom and yellow oleander.
2b	C-LD	3. It may be reasonable to administer digoxin-Fab to treat poisoning from cardiac glycosides other than digoxin, digitoxin, *Bufo* toad venom, and yellow oleander.
2b	C-LD	4. It may be reasonable to administer atropine for bradydysrhythmias caused by digoxin and other cardiac glycoside poisoning.
2b	C-LD	5. It may be reasonable to attempt electrical pacing to treat bradydysrhythmias from digoxin and other cardiac glycoside poisoning.
2b	C-LD	6. It may be reasonable to administer lidocaine, phenytoin, or bretylium to treat ventricular dysrhythmias caused by digitalis and other cardiac glycoside poisoning until digoxin-Fab can be administered.
3: No Benefit	B-NR	7. We do not recommend the use of hemodialysis, hemofiltration, hemoperfusion, or plasmapheresis to treat digoxin poisoning.

CLASS 1 (STRONG) Benefit >>> Risk

CLASS 2a (MODERATE) Benefit >> Risk

CLASS 2b (WEAK) Benefit ≥ Risk

Class 3: Harm (STRONG) Risk > Benefit

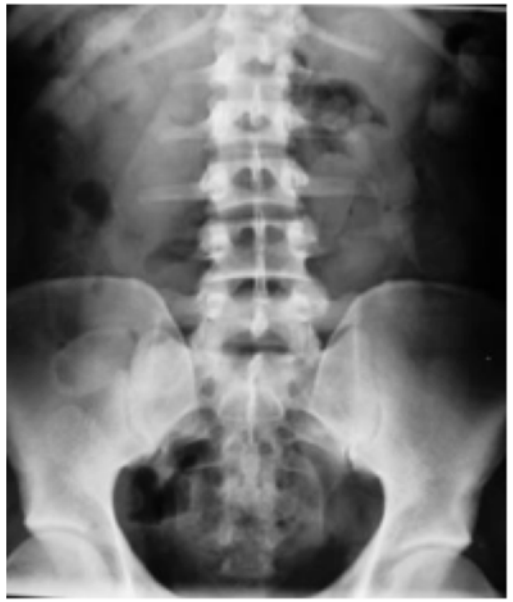
LEVEL B-NR (Nonrandomized)

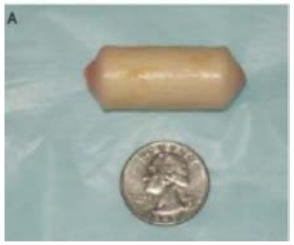
LEVEL C-LD (Limited Data)

LEVEL B-NR (Nonrandomized)

Lavonas et al, Circulation 2023

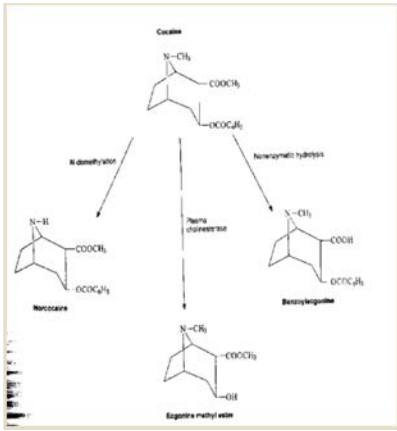
6 Cocaine poisoning





Recommendations for the Management of Patients With Life-Threatening Cocaine Poisoning

COR	LOE	Recommendation
1	C-LD	1. We recommend rapid external cooling for life-threatening hyperthermia from cocaine poisoning.
2a	C-LD	2. It is reasonable to administer sodium bicarbonate for wide-complex tachycardia or cardiac arrest from cocaine poisoning.
2a	C-LD	3. It is reasonable to administer lidocaine for wide-complex tachycardia from cocaine poisoning.
2a	C-LD	4. It is reasonable to administer vasodilators (eg, nitrates, phentolamine, calcium channel blockers) for patients with cocaine-induced coronary vasospasm or hypertensive emergencies.



Mechanisms of arrhythmia:
- Sodium channel blockade
- Potassium channel blockade
- Catecholamine excess and CNS agitation
- Myocardial ischemia and infarction

Lavonas et al, Circulation 2023

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

7

Management of Patients With Life-Threatening Sympathomimetic Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend sedation for severe agitation from sympathomimetic poisoning.
1	C-LD	2. We recommend rapid external cooling for life-threatening hyperthermia from sympathomimetic poisoning.
2a	C-EO	3. Vasodilators, such as phentolamine and/or nitrates, are reasonable for coronary vasospasm from sympathomimetic poisoning.
2a	C-EO	4. Mechanical circulatory support, such as intra-aortic balloon pump or VA-ECMO, is reasonable for cardiogenic shock from sympathomimetic poisoning refractory to other treatment measures.
3: Harm	C-LD	5. Prolonged use of physical restraint without sedation is potentially harmful.

CLASS 1 (STRONG) Benefit >>> Risk

LEVEL B-NR (Nonrandomized)

LEVEL C-LD (Limited Data)

CLASS 2a (MODERATE) Benefit >> Risk

LEVEL C-EO (Expert Opinion)

Class 3: Harm (STRONG) Risk > Benefit

Sympathomimetics: cocaine, amphetamines, cathinones, and some synthetic cannabinoid receptor …

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27e Congrès francophone
ACTUALITÉS EN RÉANIMATION
Médecine Intensive, Surveillance Continue
et Urgences Graves

Intoxications par cardiotropes : ACR et thérapeutiques d'exception (ECLS)

Dr Nicolas DEYE
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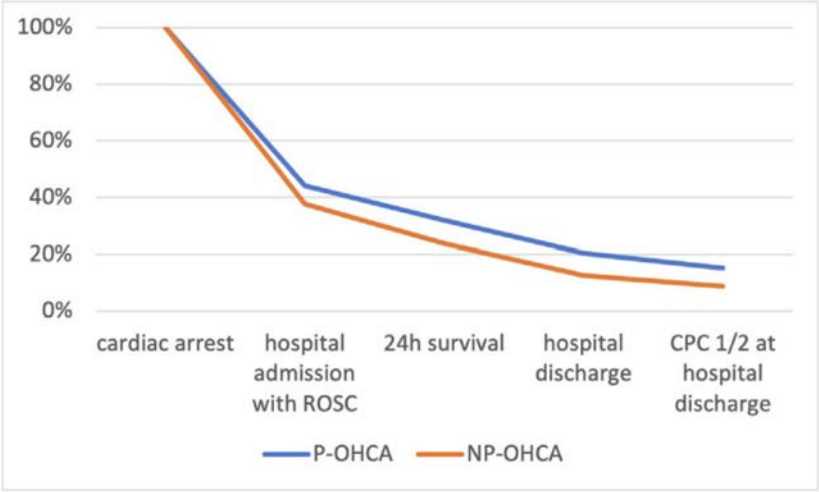
No COI

Higher chance of survival in patients with out-of-hospital cardiac arrest attributed to poisoning

Huser C, et al. Resuscitation 2022

	P-OHCA patients n = 574	NP-OHCA patients n = 40,146	
age	median (IQR)	median (IQR)	
years	42.7 (34.5; 53.8)	73.4 (61.5; 81.8)	p < 0.001
sex (missing n = 10)	n (%)	n (%)	
male	408 (71.1)	26,006 (64.8)	
female	166 (28.9)	14,130 (35.2)	p = 0.002
witnessed			
no	380 (66.2)	16,763 (41.8)	
lay person	136 (23.7)	17,760 (43.9)	
EMS	58 (10.1)	5,759 (14.4)	p < 0.001
First documented rhythm (on scene)			
VF/pVT	53 (9.2)	10,059 (25.1)	
PEA	93 (16.2)	8,238 (20.5)	
asystole	422 (73.5)	21,567 (53.7)	
unknown	6 (1.0)	282 (0.7)	p < 0.001
bystander CPR			
yes	202 (35.2)	14,152 (35.3)	p = 0.52
defibrillation at any time			
yes	101 (17.6)	14,887 (37.1)	p < 0.001
duration of CPR efforts until death (min)*			
median (IQR)	32 (22;43)	30 (20;41)	p = 0.18
missing	n = 404	n = 25,680	
duration of CPR until ROSC# (min)			
median (IQR)	15 (8;23)	18 (11;26)	p = 0.002
missing	n = 382	n = 26,944	
Hospital admission			
with ROSC	253 (44.1)	15,084 (37.6)	p = 0.001
with ongoing CPR	64 (11.1)	4291 (10.7)	p = 0.72
Survival			
at 24 hours	183 (31.9)	9538 (23.8)	p < 0.001
at hospital discharge	117 (20.4)	5027 (12.5)	p < 0.001
CPC 1/2 at hospital discharge	87 (15.2)	3531 (8.8)	p < 0.001



Poisoning = independent protective prognostic factor in multivariate analysis (OR 2.47, 95%-CI [1.71–3.57])

In P-OHCA patients with initial PEA, survival with good outcome (SFO) was comparable to initial VF (34.3 % vs. 37.7%)

In patients with asystole and CPR > 20 min, SFO = 2.0% in P-CA patients versus 0.4% in NP-CA patients.

Poisoning-related cardiac arrest: Why prognosis should be better?

Lacoste-Palasset, Mégarbane, Deye. Resuscitation 2022

	Overall, n = 400	NP-CA, n = 357	P-CA, n = 43	p
Demographics, n (%) unless otherwise stated				
Age, yo, median [IQR]*	61 [50, 73]	62 [52, 74]	48 [37, 56]	**<0.001**
Gender, female$	120 (30)	101 (28)	19 (44)	**0.04**
BMI, median [IQR]	25.7 [22.8, 29.4]	25.9 [23.0, 29.5]	24.2 [21.3, 28.0]	0.16
Hypertension	156 (40)	147 (42)	9 (21)	**0.008**
Diabetes	86 (22)	83 (24)	3 (7)	**0.01**
Heart failure	45 (12)	45 (13)	0 (0)	**0.009**
Chronic alcoholism	105 (28)	86 (26)	19 (49)	**0.004**
No Flow, median [IQR]*	2.0 [0.0, 8.0]	2.0 [0.0, 8.0]	1.0 [0.0, 7.0]	0.45
Low flow, median [IQR]*	16.0 [10.0, 27.0]	16.0 [10.0, 26.8]	15.0 [7.3, 29.0]	0.46
Witnessed arrest$	376 (94)	335 (94)	41 (95)	1
Bystander CPR	271 (68)	245 (69)	26 (61)	0.30
Initial shockable rhythm (BLS)*	155 (39)	151 (43)	4 (9)	**<0.001**
Rhythm documented by ALS team				0.02
Asystole	170 (44)	145 (42)	25 (61)§	
VF/VT	67 (17)	65 (19)	2 (5)§§	
PEA	40 (10)	34 (10)	6 (15)§§§	
ROSC	112 (29)	104 (30)	8 (20)§§§§	
No Flow, median [IQR]*	2.0 [0.0, 8.0]	2.0 [0.0, 8.0]	1.0 [0.0, 7.0]	0.45
Low flow, median [IQR]*	16.0 [10.0, 27.0]	16.0 [10.0, 26.8]	15.0 [7.3, 29.0]	0.46
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Rhythm documented by ALS team				0.02
Asystole	170 (44)	145 (42)	25 (61)§	
VF/VT	67 (17)	65 (19)	2 (5)§§	
PEA	40 (10)	34 (10)	6 (15)§§§	
Lactate on admission, median [IQR]	6.15 [3.01, 10.04]	5.78 [3.0, 9.4]	9.2 [4.7, 12.0]	**0.01**
pH upon admission, median [IQR]	7.21 [7.11, 7.31]	7.22 [7.12, 7.31]	7.11 [6.99, 7.25]	**0.001**
Catecholamine upon admission	269 (73.7)	245 (74.0)	24 (70.6)	0.68
Survival at hospital discharge	175 (43.8)	155 (43.4)	20 (46.5)	0.75
SFO at hospital discharge	145 (36.2)	130 (36.4)	15 (34.9)	1
SFO at 2-month follow-up	125 (33.2)	115/337 (34.1)	10/39 (25.6)	0.37

Non ECMO cohort

Causes of CA :
most P-CA resulted from hypoxic causes (70%) compared to NP-CA (22%).

Poisoning by
- **cardiotoxicants in 11 patients (26%): SFO 46%**,
- **psychotropic drugs in 29 (67%): SFO = 35%,**
- drug inhalation in 3 patients (7%): SFO = 0%,

Lavonas et al, Circulation 2023

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

American Heart Association.

Recommendations for the Use of VA-ECMO in Patients With Life-Threatening Poisoning

COR	LOE	Recommendations
2a	C-LD	1. It is reasonable to use VA-ECMO for persistent cardiogenic shock or cardiac arrest due to poisoning that is not responsive to maximal treatment measures.
2a	C-LD	2. It is reasonable to use VA-ECMO for persistent dysrhythmias due to poisoning when other treatment measures fail.
2b	C-EO	3. The effectiveness of VA-ECMO for poisoned patients with cardiovascular collapse from causes other than cardiogenic shock has not been established.

CLASS 2a (MODERATE) Benefit >> Risk

CLASS 2b (WEAK) Benefit ≥ Risk

LEVEL C-LD (Limited Data)

LEVEL C-EO (Expert Opinion)

Sebastian Voicu | Aymen M'Rad | Isabelle Malissin | Nicolas Deye
Bruno Mégarbane

Basic Clin Pharmacol Toxicol 2023

Refractory cardiac arrest: all types of toxicants

- ECLS decision preferably after relatively short durations of CPR (30 min or less) to optimize survival
- Do not refute based exclusively CPR duration, survival after 180 min is still possible

CCB-related shock (optimum cutoffs for all parameters not determined):

- Cardiac dysfunction on catecholamine treatment, LVEF ≤40%–50%
- High epinephrine + norepinephrine doses ≥3 μg/kg/min
- Blood lactate concentration ≥8 mmol/L

BB-related shock (optimum cutoffs for all parameters not determined):

- Cardiac dysfunction on catecholamine treatment, LVEF ≤40%–50%
- High epinephrine + norepinephrine + isoproterenol doses ≥4 μg/kg/min
- Blood lactate concentration ≥5 mmol/L

SCB-related shock (optimum cut-offs for all parameters not determined):

- Cardiac dysfunction on catecholamine treatment, LVEF ≤35%
- Epinephrine + norepinephrine doses ≥1 μg/kg/min
- Lactate concentration ≥5 mmol/L
- QRS duration ≥0.15 s

MINI REVIEW

Extracorporeal life support in cardiotoxicant poisoning—A narrative review

indications and timing were at the discretion of physicians in charge but mostly included persistent cardiovascular failure despite elevated doses of inotropic/vasopressor support associated with elevated blood lactate concentrations (usually, >5 mmol/L) and collapsed left ventricular ejection fraction (LVEF; usually, ≤40%). Survival improved using ECLS versus standard care in one study. Survival was ~80% if ECLS was implemented in refractory cardiovascular failure and 25%–66% if implemented in cardiac arrest.

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27e Congrès francophone
ACTUALITÉS EN RÉANIMATION
Médecine Intensive, Surveillance Continue
et Urgences Graves

Intoxications par cardiotropes : conclusion

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No COI

REVIEW Open Access

Management of pharmaceutical and recreational drug poisoning

Mégarbane et al
AIC 2020

Experts from SRLF, SFMU, STC, SFTA, GFRUP

RECOMMENDATION IN THE FORM OF AN EXPERT OPINION/STRONG CONSENSUS

R 8.1.1: The experts suggest that an antidote should be administered to all patients with presumed cardiotoxicant poisoning with signs of clinical or prognostic severity, according to the specific modalities of each molecule (Table 6).

Table 6 Main antidotes for cardiovascular drugs

Antidote	Toxin	Indication	Availability	Comments
Atropine	Negative chronotropic effects	Bradycardia QT prolongation	Immediate	Expert opinion
Hypertonic sodium bicarbonate	Membrane-stabilizing effects	QRS ≥ 120 ms and MAP ≤ 65 mmHg	Immediate	Expert opinion
Calcium salts	Calcium-channel blockers	HR ≤ 60 bpm MAP ≤ 65 mmHg	Immediate	Expert opinion
Catecholamine	Polyvalent	Shock	Immediate	Grade 2
Digoxin antibody Fab fragments	Digoxin		< 2 h	Grade 2
Glucagon	Beta-blockers	Bradycardia	< 2 h	Expert opinion
Isoprenaline	Beta-blockers (sotalol) Negative chronotropic effects: calcium-channel blockers	QT prolongation Torsades de pointes Bradycardia	Immediate	Expert opinion
Insulin–glucose	Calcium-channel blockers Beta-blockers	Bradycardia MAP ≤ 65 mmHg	Immediate	Expert opinion

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Lavonas et al, Circulation 2023

American Heart Association.

Top Take-home Messages for Management of Patients with Cardiac Arrest or Life-threatening Toxicity Due to Poisoning

1. Treatment of cardiac arrest and life-threatening toxicity due to poisoning often requires specialized treatments that most clinicians do not use frequently such as antidotes and venoarterial extracorporeal membrane oxygenation, in addition to effective basic and advanced life support. Timely consultation with a medical toxicologist, clinical toxicologist, or regional poison center facilitates rapid and effective therapy.

3. High-dose insulin therapy is recommended early in the treatment of patients with life-threatening β-blocker and calcium channel blocker poisoning.

4. Standard advanced life support with the addition of administration of sodium bicarbonate is appropriate for the treatment of life-threatening dysrhythmias caused by cocaine or other sodium channel blockers.

6. Administration of digoxin-specific immune antibody fragments can reverse life-threatening dysrhythmias from digoxin poisoning.

7. Use of 20% intravenous lipid emulsion can be efficacious in the resuscitation of life-threatening local anesthetic toxicity, especially from bupivacaine.

10. Venoarterial extracorporeal membrane oxygenation can be lifesaving for patients with cardiogenic shock or dysrhythmias that are refractory to other treatment measures. Because venoarterial extracorporeal membrane oxygenation implementation takes time, the process should be started early in patients who are not responding well to other therapies.

Knowledge Gaps and Priorities of Research

β-Blockers and CCBs

Does high-dose insulin therapy, administered in addition to or instead of standard vasopressors, reduce mortality or ischemic complications?

What is the ideal vasopressor or inotropic strategy for refractory shock from β-blocker or CCB overdose? Does tailoring therapy to cardiogenic vs vasoplegic shock improve outcomes? Are nonadrenergic vasopressors effective?

What are the benefits of glucagon for β-blocker poisoning?

What are the benefits of glucagon for CCB poisoning?

Is hemodialysis beneficial for atenolol, sotalol, or nadolol poisoning?

What are the benefits of ILE for oral overdose of lipophilic β-blockers or CCBs?

What are the benefits of gastrointestinal decontamination in patients with life-threatening β-blocker or CCB poisoning, particularly when extended-release formulations are involved?

Cocaine

What is the ideal management of cocaine-induced myocardial ischemia, hypertensive emergency, or dysrhythmia?

Cyanide

Does the addition of sodium thiosulfate to either hydroxocobalamin or sodium nitrite therapy improve outcomes in cyanide-poisoned patients?

Digoxin

What is the best empirical dose of digoxin-Fab for patients with cardiac arrest from digoxin poisoning?

What is the appropriate dose of digoxin-Fab for patients with critical poisoning from cardiac glycosides other than digoxin?

LAs

What is the benefit of ILE when given in addition to standard resuscitation with vasopressors and sodium bicarbonate for patients with LA cardiotoxicity?

What is the ideal dose of ILE for LA poisoning?

Is the optimal treatment for poisoning from other LAs the same as for poisoning from bupivacaine?

Sodium channel blockers

What is the ideal treatment for poisoning from sodium channel blockers other than TCAs?

What physiological or electrocardiographic targets are most appropriate for patients with sodium channel blocker to prevent deterioration to cardiac arrest?

Sympathomimetics

What factors predict which patients with severe sympathomimetic poisoning will suddenly decompensate to cardiac arrest?

What is the ideal medication or combination of medications for sedation of patients with severe psychomotor agitation?

Role of VA-ECMO

Which patients with poisoning have improved outcomes from VA-ECMO compared with standard critical care plus antidotal therapy?

In what situations can VA-EMCO benefit patients with distributive shock or cellular injury from poisoning?

What is the optimal timing of VA-ECMO initiation? Are outcomes better when VA-ECMO is initiated in the periarrest period, or earlier in the course of illness?