Management of severe poisonings with cardiotoxicants

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Poisonings with cardiotoxicants

- In the USA: AAPCC 2008
  Cardiovascular agents: 10th cause of exposures (3.7%) but 4th cause of death (fatality rate: 0.27%)

- As usual no European data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poisoned patients</td>
<td>1,554</td>
<td>60 (4 %)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>164 (11 %)</td>
<td>37 (22 %)</td>
</tr>
</tbody>
</table>

January 1998 to October 2002
3,922 patients

Lariboisière Hospital ICU, Paris, France
**Cardiotoxicants**

A larger entity than cardiovascular drugs

- **Cardiovascular pharmaceuticals**
  - Sodium-channel blockers (Class I)
  - Beta-blockers (class II)
  - Potassium channel blockers (sotalol) (class III)
  - Calcium-channel antagonists (class IV)
  - Cardioglycosides (class V)

- **Non-cardiovascular pharmaceuticals:**
  antipsychotics, antidepressants, antihistamines, ...

- **Drugs:** cocaine, amphetamines, ...

- **Rural toxicants:** organophosphates, pesticides, ...

- **Industrial toxicants:** alumine phosphide, ...

- **Household toxicants:** trichloroethylene, ...

- **Plants:** digitalis, aconit, colchicine, yew, Taxus baccata...

- **Over-the-counter:** « Best life » (sibutramine)
The prognostic value of the ingested dose: The example of ajmaline poisoning

Delay for symptom occurrence: 1 - 3 h
All patients in cardiac arrest died

<table>
<thead>
<tr>
<th>Ingested tablets</th>
<th>N</th>
<th>Cardiac arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>2 g</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>3 g</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

Conso F. *Press Med* 1980
The prognostic value of plasma cardiotoxiant concentrations in acute poisonings

Flecainide poisonings

Outcome of Acute Poisonings

Survivors | Fatalities
---|---
Outcome

Plasma Flecainide Concentrations (mg/L)

Survivors

Fatalities

Verapamil poisonings

Serum verapamil concentrations (µM)

Survivors | Fatalities
---|---
Outcome

Mégarbane B. Clin Tox 2007

Mégarbane B. BCPT 2010
Specific drug-dependent considerations to assess the risk and features of the intoxicated heart
Beta-blocker poisonings (1)

Clinical features

Sinus bradycardia or AV blocks

Other signs:
- Hypotension, collapse
- Bronchospasm
- Respiratory depression
- Drowsiness, seizures, coma
- Hypoglycemia, hyperkaliemia

Love JN. *J Toxicol Clin Toxicol* 1997

*Table: Dysrhythmias Reported in 23 Beta Blocker Fatalities*

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>15</td>
</tr>
<tr>
<td>Asystole</td>
<td>10</td>
</tr>
<tr>
<td>Electrical-mechanical dissociation</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>4</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>3</td>
</tr>
<tr>
<td>Idioventricular rhythm</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>2</td>
</tr>
<tr>
<td>Third degree heart block</td>
<td>1</td>
</tr>
</tbody>
</table>

Multiple dysrhythmias were reported in some patients.
Beta-blocker poisonings (2)
Excess mortality in case of membrane stabilizing activity

<table>
<thead>
<tr>
<th>Beta Blocker</th>
<th># Exposures</th>
<th>% Total Exposures</th>
<th># Deaths</th>
<th>% Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol*</td>
<td>22,334</td>
<td>43.9</td>
<td>27</td>
<td>71.1</td>
</tr>
<tr>
<td>Atenolol</td>
<td>13,587</td>
<td>26.7</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>7,511</td>
<td>14.8</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Nadolol</td>
<td>2,762</td>
<td>5.4</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>1,907</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pindolol*</td>
<td>742</td>
<td>1.5</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Timolol</td>
<td>686</td>
<td>1.4</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Acebutolol*</td>
<td>584</td>
<td>1.1</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>373</td>
<td>&lt;1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>226</td>
<td>&lt;1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Penbutolol*</td>
<td>72</td>
<td>&lt;1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Sotalol</td>
<td>48</td>
<td>&lt;1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Others</td>
<td>29</td>
<td>&lt;1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1,295</td>
<td>2.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>52,156</strong></td>
<td></td>
<td><strong>40</strong></td>
<td></td>
</tr>
</tbody>
</table>

Two cases involved mixed ingestions of propranolol and atenolol. *Nonspecific membrane activity.

Love JN. J Toxicol Clin Toxicol 1997
**Beta-blocker poisonings (3)**

Excess morbidity in case of cardioactive coingestants (calcium channel blocker, cyclic antidepressant, neuroleptics)

<table>
<thead>
<tr>
<th>Beta Blocker</th>
<th>Number of Exposures</th>
<th>Cardiovascular Morbidity</th>
<th>Exposures Without Cardioactive Coingestants</th>
<th>Number of Exposures</th>
<th>Cardiovascular Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Propranolol</em></td>
<td>121 (43%)</td>
<td>19 (46%)</td>
<td>85 (44%)</td>
<td>8 (50%)</td>
<td></td>
</tr>
<tr>
<td><em>Metoprolol</em></td>
<td>36 (13%)</td>
<td>7 (17%)</td>
<td>23 (12%)</td>
<td>4 (25%)</td>
<td></td>
</tr>
<tr>
<td><em>Labetalol</em></td>
<td>12 (4%)</td>
<td>3 (7%)</td>
<td>10 (5%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td><em>Acebutolol</em></td>
<td>4 (1%)</td>
<td>1 (2%)</td>
<td>3 (2%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td><em>Pindolol</em></td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>87 (31%)</td>
<td>8 (20%)</td>
<td>61 (32%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>8 (3%)</td>
<td>2 (5%)</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5 (2%)</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>2 (&lt;1%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>280</td>
<td>41</td>
<td>193</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Love JN. *J Toxicol Clin Toxicol* 2000
Calcium-channel antagonist poisonings (1)
Toxicological consequences of pharmacological properties

Five different CCB classes, including dihydropyridines (nefidipine and amlodipine), phenylalkylamine (verapamil), benzothiazepine (diltiazem), diphenylpiperazine (mibefradil), and diarylaminopropylamine (bepridil).

Dihydropyridines: Selective vasodilators
- Peripheral vasodilation
- Potential reflex increase in HR, myocardial contractility and \(O_2\) demand

Non-dihydropyridines: equipotent for cardiac tissue and vasculature
- Heart rate moderating
- Peripheral and coronary vasodilation
- AV conduction dysfunction
- Reduced inotropism

Harris NS. *N Eng J Med* 2006
## Calcium-channel antagonist poisonings (2)
### Features and severity

<table>
<thead>
<tr>
<th></th>
<th>Verapamil (N = 68)</th>
<th>Diltiazem (N = 27)</th>
<th>Nifedipine (N = 14)</th>
<th>Total (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>79%</td>
<td>89%</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Bradycardia (&lt; 60 /min)</td>
<td>56%</td>
<td>78%</td>
<td>43%</td>
<td>60%</td>
</tr>
<tr>
<td>Severe bradycardia (&lt; 40 /min)</td>
<td>24%</td>
<td>26%</td>
<td>43%</td>
<td>60%</td>
</tr>
<tr>
<td>AV block</td>
<td>60%</td>
<td>63%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Complete AV block</td>
<td>53%</td>
<td>52%</td>
<td>21%</td>
<td>51%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>21%</td>
<td>22%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Death rate</td>
<td>25%</td>
<td>7%</td>
<td>7%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Sauder P. Intoxications aiguës. Elsevier, 1999
Poisonings with sodium channel blockers (1)  

Molecules

- **Polycyclic antidepressants**, citalopram and venlafaxin
- **Quinine** and chloroquine
- **Class I anti-arrhythmics** (quinidine, cibenzoline, flecainide, propafenone)
- **Some β-blockers** like propranolol and acebutolol
- **Carbamazepine**
- **Propoxyphene**
- **Cocaine**

![Diagram of sodium channel blockers](image)
Poisonings with sodium channel blockers (2)

Clinical features

- **Cardiovascular syndrome:**
  - **ECG**: QRS enlargement, QT prolongation, AV blocks
  - **Circulation**: Cardiogenic and vasoplegic shock

- **Metabolic syndrome**: Hypokaliemia, lactic acidosis

- **Neurological syndrome**: Convulsive coma

- **Respiratory syndrome**: Delayed ARDS with alveolar hemorrhage
Poisonings with sodium channel blockers (3)

Value of QRS to predict arrhythmias in tricyclic antidepressant poisonings

<table>
<thead>
<tr>
<th>QRS duration (msec)</th>
<th>Seizure risk</th>
<th>Ventricular dysrhythmia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>100 - 160</td>
<td>moderate</td>
<td>mild</td>
</tr>
<tr>
<td>&gt; 160</td>
<td>elevated</td>
<td>elevated</td>
</tr>
</tbody>
</table>

Measurement of the terminal 40-millisecond frontal plane axis


Sanaei-Zadeh H. *Resuscitation* 2011
Prevalence: 15% tricyclic AD poisonings
Disappears if < 1 µmol/l
Response to NaHCO₃ controversial
Associated to genetic polymorphism (cocaine)

<table>
<thead>
<tr>
<th>J wave amplitude</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 2 mm</td>
<td>≥ 2 mm</td>
<td>≥ 2 mm</td>
</tr>
<tr>
<td>T wave</td>
<td>Negative</td>
<td>Positive or biphasic</td>
<td>Positive</td>
</tr>
<tr>
<td>ST-T configuration</td>
<td>Coved type</td>
<td>Saddleback</td>
<td>Saddleback</td>
</tr>
<tr>
<td>ST segment (terminal portion)</td>
<td>Gradually descending</td>
<td>Elevated ≥ 1 mm</td>
<td>Elevated &lt; 1 mm</td>
</tr>
</tbody>
</table>

Goldgran-Tolédano D. NEJM 2002
Monteban-Kooistra WE. Intensive Care Med 2005
Cocaine poisoning:

Mechanisms of arrhythmia genesis:
- Sodium channel blockade
- Potassium channel blockade
- Catecholamine excess and SNC agitation
- Myocardial ischemia and infarction
**Cardioglycoside poisonings (1)**

**Clinical features of digitalis poisoning**

Na/K - ATPase blockade

Circumstances: therapeutic overdose > suicide

Multiple and mostly nonspecific manifestations

Fatigue, blurred vision, disturbed color perception

Anorexia, nausea, vomiting, diarrhea, abdominal pain

Headache, dizziness, confusion, delirium, and occasionally hallucinations

Rarely intestinal none occlusive infarction

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

Cardiac arrhythmias may take almost any form and are responsible for mortality
**Cardioglycoside poisonings (2)**

Typical ECG in digitalis poisoning

Combination of SVT + AV block is highly suggestive of digitalis toxicity

**Harmless**  
Sinus-bradycardia, ST-scoop, AVB I

**Less harmless**  
AVB II, bigeminus, PAT

**Dangerous**  
AVB III, Polytope ventricular extrasystolia, VT

**Near death**  
VF, asystolia
Cardioglycoside poisonings (3)

ECG features

<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>SAB</th>
<th>AVB 1</th>
<th>AVB 2</th>
<th>AVB 3</th>
<th>VT/VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taboulet, %</td>
<td>17</td>
<td>26.8</td>
<td>12.2</td>
<td>9.8</td>
<td>14.6</td>
<td>9.7</td>
</tr>
<tr>
<td>N=141</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapostolle, %</td>
<td>25.7</td>
<td>24.2</td>
<td>10.6</td>
<td>14.3</td>
<td>19.7</td>
<td>9.1</td>
</tr>
<tr>
<td>N=141</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation with ventricular response <50/min
BSA III: Sinoatrial block of third degree
AVB I / II / III: Atrioventricular block of first, second or third degree

Taboulet P. Clin Toxicol 1993
Lapostolle F. Crit Care Med 2009
Main prognostic factors

<table>
<thead>
<tr>
<th>Age</th>
<th>AV block</th>
<th>K+ &gt;4.5</th>
<th>Death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>49</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>18</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>29</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>38</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>No</td>
<td>Yes</td>
<td>74</td>
</tr>
<tr>
<td>&gt; 55</td>
<td>Yes</td>
<td>No</td>
<td>35</td>
</tr>
</tbody>
</table>

Dally S. Press Med 1981
Drugs associated with QT-prolongation and torsade-de-pointes

Drug-drug interactions (P-450 inhibitors) > overdoses +/- genetic vulnerability (hereditary long QT) or cardiac disease

- Antiarrhythmics (class Ia, Ic, III, V)
- Sympathomimetics
- Methadone
- Antipsychotics & Antidepressants (phenothiazines, atypical antipsychotics tricyclics, tetracyclics, SSRIs)
- Antihistamines (terfenadine, astemizole, loratadine)
- Gastrointestinal agents (cisapride, domperidone, dolasetron)
- Antiinfectives & antifungals (macrolides, fluoroquinolones, azoles)
The QT nomogram is a clinically relevant risk assessment tool that accurately predicts arrhythmogenic risk for drug-induced QT prolongation

Chan A. QJM 2007
Management of drug-induced cardiac failure and arrhythmias
Strategy of management of toxic cardiovascular failure

- Diagnosis of shock
- Determination of the mechanism of shock
- Definition of the optimal treatment
- Diagnosis of the refractoriness of shock
Assessment of the mechanism of the toxic shock

1- Hypotension: systolic BP < 90 mm Hg or systolic BP decrease > 40 mmHg or mean BP < 65 mmHg
2- Unresponsive to fluids
3- At least one sign of organ hypoperfusion
**Consequences of convulsion-induced hypoxemia and acidosis on cardiac toxicity**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Just after</th>
<th>3h later</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial pH</strong></td>
<td>7.39</td>
<td>7.19</td>
<td>7.46</td>
</tr>
<tr>
<td><strong>Lactate concentration</strong></td>
<td>1.7</td>
<td>6.5</td>
<td>3.1</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PaO$_2$ (mmHg)</strong></td>
<td>95</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>120</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td><strong>QRS width (s)</strong></td>
<td>0.08</td>
<td>0.13</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Taboulet P. *Réan Urg* 1993
**Conventional supportive treatments in ICU**

- **Intubation and mechanical ventilation:**
  - Severe arrhythmias and associated collapse
  - Coma, convulsions, respiratory failure

- **Treatment of collapse/shock**
  - Fluids + adequate catecholamines

- **Treatment of torsade-de-pointes**
  - Defibrillation, MgSO₄, titrated isoproterenol, cardiac pacing
  - Correction of electrolyte imbalance \((K^+, Mg^{2+})\)

- **Treatment of monomorphic ventricular tachycardia**
  - Defibrillation, MgSO₄, lidocaine infusion

- **Cardiac pacing**
  - High degree AV block with preserved inotropism
# Chloroquine poisoning: prognosis assessment

<table>
<thead>
<tr>
<th>Supposed ingested dose</th>
<th>Systolic BP</th>
<th>QRS duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe</strong></td>
<td>&gt; 4 g</td>
<td>&lt; 100 mmHg or</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>2 - 4 g</td>
<td>≥ 100 mmHg and</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>&lt; 2 g</td>
<td>≥ 100 mmHg and</td>
</tr>
</tbody>
</table>

**Severe poisoning:**
- Epinephrine 0.25 μg/kg/min with increasing 0.25 μg/kg/min steps to obtain SBP ≥ 100 mmHg
- Intubation and mechanical ventilation
- Diazepam 2 mg/kg in 30 min followed with 2-4 mg/kg/24h


*Riou B. N Engl J Med 1988*
Place of GI decontamination and elimination enhancement

- Activated charcoal: within 2 h following the ingestion

- Repeated doses of charcoal: Low-sustained forms

- Dialysis: limited interest as
  • Elevated protein binding
  • Elevated distribution volume
  • Liposolubility
  • Elevated endogenous clearance
Risk reduction in escitalopram-related QT prolongation with charcoal

Van Gorp F. Br J Clin Pharm 2011

Moderate reduction in the risk of abnormal QT interval with SDAC

Dose-related lengthening of the QT interval lagging the increase in drug concentration.
Antidotes for beta-blocker poisonings

Specific treatments

We recommend if supportive measures (adequate fluids and atropine) are ineffective, the administration of antidotes in the following order: dobutamine (or isoprenaline, especially in sotalol intoxication), glucagon, and epinephrine.

Taboulet P. Clin Toxicol 1993
Antidotes for the calcium-channel blocker poisonings

- **Calcium salts:** 1 g IV bolus /15-20 min, 4 doses followed with 20-50 mg/kg/h infusion
- **Glucose - insulin:** 1 UI/kg IV bolus followed with 0.5-1 UI/kg/h infusion + adequate glucose

Metabolic basis for myocardial beneficial effect:
- Increase of insulin pancreas secretion
- Decrease of insulin resistance
- Decrease of free fatty acid uptake and switch to carbohydrates
- Increase of cytoplasmic calcium concentration
- Increase of myocardial “oxygen delivery / work” ratio

Yuan TH. *J Toxicol Clin Toicol* 1999

Kline JA. *Toxicol Appl Pharmacol* 1997
The exact mechanism, optimal dosing, and mode of infusion are not well defined.

The most common approach: 1mEq/kg IV bolus if widened QRS or dysrhythmia.

Repeat boluses /3–5 min or place continuous infusion to achieve resolution of the dysrhythmia or QRS narrowing.

Serum pH should not exceed 7.55.
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
- Other toxin-specific mechanisms?
Is pacing still appropriate in digitalis poisonings?

92 acute digitalis poisoning (1983-1990)
51 treated with cardiac pacing ± Fab fragments
(14 digoxin / 36 digitoxin / 1 mixed; no significant differences)

<table>
<thead>
<tr>
<th>Method</th>
<th>Number</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing alone</td>
<td>23</td>
<td>17%</td>
</tr>
<tr>
<td>Fab alone</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td>Pacing + Fab</td>
<td>16</td>
<td>31%</td>
</tr>
</tbody>
</table>

Taboulet P. *Clin Toxicol* 1993
**Indication & dosage regimen of Fab fragments**

**Life-threatening conditions**
- Ventricular arrhythmia: VF or VT
- Bradycardia with HR ≤ 40 /min despite atropine infusion (1 mg)
- Hyperkalemia > 5 mmol /L
- Cardiogenic shock
- Mesenteric infarction

**Poor prognosticicators**
- Male
- Age over 55 years
- Underlying heart disease
- Atrioventricular block
- Bradycardia with HR < 60 /min despite atropine infusion (1 mg)
- Hyperkalemia > 4.5 mmol /L

**Molar neutralization for curative treatment**

**Half-molar neutralization for prophylactic treatment**
Curative/prophylactic strategy of Fab fragments administration (N = 141)

First-line therapy with Fab fragments in patients with digitalis poisoning was associated with a low mortality rate (7.5%) without increase in cost, vial number, and duration of ICU stay.
Non-responsiveness to conventional supportive treatments and antidotes
Difficulty to manage catecholamines
- epinephrine versus dobutamine -

F, 17 years, severe propranolol poisoning
Sedation + mechanical ventilation + FiO₂ 100%

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine 1.5 mg/h</th>
<th>Dobutamine 15 µg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>93</td>
<td>56</td>
</tr>
<tr>
<td>D</td>
<td>64</td>
<td>33</td>
</tr>
<tr>
<td>M</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td><strong>P_{RA}</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>P_{AP}</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>D</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td><strong>P_{cw}</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiac Index</strong></td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Systemic resistances</strong></td>
<td>50.3</td>
<td>20.3</td>
</tr>
</tbody>
</table>

30 min later

Dramatic decrease in BP ...
Fatal poisonings with cardio toxic agents despite optimal pharmacological management in ICU

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>N</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>63</td>
<td>27%</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>40</td>
<td>28%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>23</td>
<td>22%</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>8</td>
<td>50%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>3</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>137</td>
<td><strong>28%</strong></td>
</tr>
</tbody>
</table>

Cause of death: Refractory ventricular fibrillaton  
Refractory asystole  
Refractory cardiogenic shock  
Brain anoxia  
ICU-acquired complications
ECLS in cardiogenic shock

The purpose of ECLS is to take over heart function until recovery can occur, minimizing myocardial work, improving organ perfusion, and maintaining the renal and biliary elimination of the toxicant.

Baud FJ. Crit Care 2007
Cannulation of femoral vessels in medical ICU

Femoral artery
Femoral vein
Femoral arcade

Mégarbane B. Intensive Care Med 2007
ECLS monitoring in ICU

Spontaneous cardiac rhythm

ECLS completely dependent cardiac flow (around 5-6 l/min)

Severe hypotension despite high dose catecholamine

Spontaneous cardiac flow
Monitoring of an ECLS-treated poisoned patient in ICU

- Efficient anticoagulation: heparin to obtain ACT = 2N
- Catecholamines for mean BP = 60-70 mmHg + dobutamine to facilitate LV discharge
- Adequate transfusions
- Adapted Mechanical ventilation
- Temperature control
- Canulated lower limb monitoring (NIRS)
- Echocardiography: weaning criteria
- Neurological evaluation (EEG, clinical)
- Care, nursing
Outcome of 57 poisoned patients treated with ECLS

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 57)</th>
<th>Cardiac failure (N = 26)</th>
<th>Refractory arrest (N = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (28%)</td>
<td>12 (46%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Neurological sequellae</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhagic accidents</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Thombo-embolic complications</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lower limb ischemia</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Multivariate analysis of the prognostic factors of death in 57 poisonings treated with ECLS

ECLS indication for refractory cardiac arrest, plasma AST level, and plasma bicarbonate concentration were the 3 independent predictive factors of death ($p < 0.0001$)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cardiac arrest</td>
<td>5.8</td>
<td>[1.6 - 21.3]</td>
</tr>
<tr>
<td>AST &gt; 750 IU//l</td>
<td>9.0</td>
<td>[1.1 - 75.2]</td>
</tr>
<tr>
<td>Plasma bicarbonate concentration &lt; 16.0 mmol/l</td>
<td>11.8</td>
<td>[1.4 - 97.4]</td>
</tr>
</tbody>
</table>
Cardiovascular collapse or shock is a life-threatening complication. Determination of the underlying mechanism (hypovolemia, vasodilatation, contractility disorders) is essential to guide the treatment. In severe poisonings, invasive or noninvasive hemodynamic investigations are warranted.

When conventional treatments fail in patients with persistent circulatory arrest or refractory shock, ECLS should be considered.

SRLF expert recommendations. Réanimation 2006
Conclusions:

- Shock and arrhythmias following poisonings with cardiotoxicants (especially with digitalis, sodium-channel, and calcium channel blockers) are frequent and may lead to life-threatening symptoms and death.

- Adequate monitoring of severity and assessment of prognostic criteria are mandatory to improve patient management.

- Treatment is mainly supportive. Despite the absence of high-level of evidence, administration of antidotes is life-saving.

- Peripheral ECLS may represent the unique solution in patients admitted for severe poisonings with non-responding arrhythmias or cardiac arrest. Its definitive benefit should be prospectively evaluated on a larger cohort.