Antidotes to manage severe poisonings

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Treatment of poisonings

The classic treatment paradigm in clinical toxicology includes:

1- Supportive treatments
2- Prevention of the toxicant absorption
3- Enhancement of the toxicant elimination
4- Specific treatments including antidotes

• Supportive treatments correct life-threatening organ failures, but do not modify the poisoning duration.

• Usually, if correctly performed, supportive treatments are sufficient to obtain a favorable outcome
Limitations of GI decontamination: A randomized controlled trial of multiple dose activated charcoal in acute self-poisoning

No benefit from routine administration of one or multiple dose activated charcoal for acute self-poisoning, nor from early administration of charcoal.
Limitations of hemodialysis to remove the toxicant

- MW < 500 D
- Water solubility and low steric hindrance
- Poor binding to plasma proteins: <60%
- Small volume of distribution <1 l/kg
- Low endogenous clearance <4 ml/min
- Single - compartment kinetics

➔ Only 0.04% of poisonings require renal extracorporeal support.
➔ Extracorporeal renal support is indicated in only limited severe poisonings (salicylates, lithium, toxic alcohols and metformin).
➔ When required, the technique should be available within a short time.
Definition of an antidote

A conventional definition:
"A remedy to counteract the effects of a poison."

A more restrictive definition:
"A pharmaceutical with assessed mechanism of action, able to modify either the pharmacokinetics or the pharmacodynamics of the poison and whose administration reliably results in significant benefit"

New toxicants  Need of new antidotes (Orphan)
Activated charcoal
Atropine
OHB12 (or other CN antidotes)
Naloxone
Methylene blue
Glucagon
Ethanol
Pyridoxine
Ipecac
Oximes
digoxin Fab fragments
Physostigmine
Fomepizole
Vitamin K
deferoxamine
Acetylcysteine
European viper antivenom
Folinic acid
Cathartics
Heavy metals chelators
Prussian blue

Availability of antidotes in the Emergency Departments of the European hospitals for immediate administration

EAPCCT, 2006
However, there is still a lack of evidence regarding the efficacy of the majority of the currently used antidotes.
# Mechanism of antidote action

<table>
<thead>
<tr>
<th>Toxicokinetic action</th>
<th>Toxicodynamic action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alters the evolution of poisoning</td>
<td>No effect on poisoning duration</td>
</tr>
<tr>
<td>No effect on the current severity of poisoning</td>
<td>Decreases the current severity of poisoning</td>
</tr>
</tbody>
</table>
Which end-point to evaluate an antidote?

**Toxicokinetic antidote**

1. Decrease of the toxicant bioavailability
2. Tissue redistribution of the toxicant
3. Promotion of the toxicant elimination in an unchanged form
4. Slowing the metabolic activation pathways of the toxicant
5. Acceleration of the metabolic deactivation pathways of the toxicant

**Toxicodynamic antidote**

6. Displacement (competitive or non-competitive) of the toxicant from its binding site
7. By-pass of the toxicant binding to the receptor
8. Correction of the peripheral effects of the toxicant
Modifying toxicokinetics with antidotes

Scherrmann JM. ClinToxicol 1989
Antidotes in the presumed poisoning-related coma
Whom should we intubate?

Certainly, poisoned patients with:

- Consciousness impairment + alteration of gag reflex
- Acute respiratory failure not responding to oxygen
- Severe cardiovascular failure
- Refractoriness to pharmacological therapies (seizures, hyperthermia)

However, probably not all poisoned patients ...

Administration of antidotes (like naloxone and flumazenil) are possible in selected patients with neurological impairment, taking into account their contraindications and recommended conditions of use.

French National Guidelines, Reanimation 2006
Naloxone: pharmacology properties

- Pure opioid antagonist at mu (high affinity), kappa, and delta receptors
- No agonist properties
- High first-pass metabolism (poor oral bioavailability)
- Short-plasma half-life: 50 min
- Duration of action: 1-4 h
- Administered IV, IM, SC, IN

Widely used to reverse opioid toxicity
Dose-dependent reversal of opioid agonist effects
Numerous studies assessing best route of administration
High dose may precipitate acute opioid withdrawal syndrome
All opioids produce a similar toxidrome in excessive dosing:

Supportive care

One antidote: Naloxone

however, pattern of opioid abuse is various and changing.

Boyer EW. NEJM 2012
Onset and duration of action in therapeutic dosing and overdose of selected opioid analgesic agents

- Methadone
- Morphine
- Buprenorphine
- Oxycodone (extended release)
- Fentanyl
- Naloxone (after administration of single dose)

- Therapeutic dose
- Overdose

Boyer EW. NEJM 2012
# Particularities of BUP overdoses

<table>
<thead>
<tr>
<th></th>
<th>Heroin (N = 26)</th>
<th>Buprenorphine (N = 39)</th>
<th>Methadone (N = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicide</strong></td>
<td>12%</td>
<td>18%</td>
<td>58%</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Co-ingestions</strong></td>
<td>73%</td>
<td>95%</td>
<td>89%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Glasgow Coma Score</strong></td>
<td>5 [3 - 9]</td>
<td>7 [4 - 10]</td>
<td>4 [3 - 10]</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>SpO₂ (%)</strong></td>
<td>82 [64 - 95]</td>
<td>94 [87 - 98]</td>
<td>91 [82 - 97]</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.29 [7.17-7.34]</td>
<td>7.35 [7.24-7.38]</td>
<td>7.33 [7.23-7.42]</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>PaCO₂ (mmHg)</strong></td>
<td>51 [45 - 55]</td>
<td>50 [45 - 66]</td>
<td>50 [36 - 57]</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong></td>
<td>46%</td>
<td>41%</td>
<td>47%</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Response to naloxone</strong></td>
<td>81%</td>
<td>0%</td>
<td>71%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Response to flumazenil</strong></td>
<td>0%</td>
<td>87%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mégarbâne B. JSAT 2010*
Naloxone Dosing

Total dose = 32 mg naloxone
= 80 vials

Boyer EW. NEJM 2012
Community-based opioid overdose prevention programs providing naloxone

Narcan is packaged with a medicine vial, syringe barrel, and a nasal atomizer

- Place the assembled Narcan atomizer in one nostril.
- Press firmly on the base of the glass vial, spraying half of the Narcan dose deep into the nasal cavity.
- Do the same in the other nostril.

<table>
<thead>
<tr>
<th>Number of programs of naloxone distribution</th>
<th>Number of naloxone vials distributed over one year</th>
<th>Number of program participants</th>
<th>Number of reported opioid overdose reversals</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>38 860</td>
<td>53 032</td>
<td>10 171</td>
</tr>
</tbody>
</table>

CDC. MMWR Morb Mortal Wkly Rep 2012
Respiratory insufficiency in benzodiazepine-induced coma

Correction of respiratory impairments using flumazenil

Gueye P. J Toxicol Clin Toxicol 2002
Should we use flumazenil in presumed toxic coma? (1)

Patient's awakening

<table>
<thead>
<tr>
<th>Study</th>
<th>Flumazenil n/N</th>
<th>Placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Sullivan 1987</td>
<td>19/31</td>
<td>6/29</td>
<td>30.24, 2.96</td>
<td>30.24</td>
<td>2.96 [1.38, 6.37]</td>
</tr>
<tr>
<td>Spivey 1993</td>
<td>48/87</td>
<td>10/83</td>
<td>43.24, 4.58</td>
<td>43.24</td>
<td>4.58 [2.48, 8.44]</td>
</tr>
<tr>
<td>Hojer 1990</td>
<td>27/53</td>
<td>3/52</td>
<td>15.29, 8.83</td>
<td>15.29</td>
<td>8.83 [2.85, 27.33]</td>
</tr>
<tr>
<td>Ritz et al. 1995</td>
<td>6/13</td>
<td>0/10</td>
<td>2.75, 10.21</td>
<td>2.75</td>
<td>10.21 [0.64, 162.34]</td>
</tr>
<tr>
<td>Weinbroum 1996</td>
<td>14/17</td>
<td>1/14</td>
<td>5.72, 11.53</td>
<td>5.72</td>
<td>11.53 [1.72, 77.20]</td>
</tr>
<tr>
<td>Barnett 1999</td>
<td>19/41</td>
<td>0/22</td>
<td>2.76, 21.36</td>
<td>2.76</td>
<td>21.36 [1.35, 337.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>242</td>
<td>210</td>
<td>100.00, 4.99</td>
<td>100.00</td>
<td>4.99 [3.14, 7.92]</td>
</tr>
</tbody>
</table>

Total events: 133 (Flumazenil), 20 (Placebo)
Test for heterogeneity: Chi² = 5.46, df = 5 (P = 0.36), I² = 8.4%
Test for overall effect: Z = 6.82 (P < 0.00001)

CGS improvement

<table>
<thead>
<tr>
<th>Study</th>
<th>Flumazenil Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett 1999</td>
<td>19 11.89 (4.10)</td>
<td>22 8.60 (3.60)</td>
<td>45.87, 0.82</td>
<td>45.87</td>
<td>0.82 [0.18, 1.46]</td>
</tr>
<tr>
<td>Spivey 1993</td>
<td>48 12.25 (2.56)</td>
<td>10 9.50 (2.75)</td>
<td>37.51, 1.05</td>
<td>37.51</td>
<td>1.05 [0.34, 1.76]</td>
</tr>
<tr>
<td>Ritz 1988</td>
<td>12 10.70 (2.70)</td>
<td>12 5.50 (1.80)</td>
<td>16.66, 2.13</td>
<td>16.66</td>
<td>2.13 [1.06, 3.19]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>80</td>
<td>42</td>
<td>106.00, 1.12</td>
<td>106.00</td>
<td>1.12 [0.69, 1.56]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 4.32, df = 2 (P = 0.12), F = 53.7%
Test for overall effect: Z = 5.06 (P < 0.00001)
Should we use flumazenil in presumed toxic coma? (2)

Major ADR

Anxiety

Vomising

Minor ADR

Ngo AS. Resuscitation 2007
Flumazenil does not increase the global costs of patient management in the ICU

<table>
<thead>
<tr>
<th>Factor</th>
<th>Flumazenil</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Emergency room</td>
<td>244 ± 106</td>
<td>276 ± 111</td>
<td>NS</td>
</tr>
<tr>
<td>Nursing</td>
<td>140 ± 59</td>
<td>151 ± 51</td>
<td>NS</td>
</tr>
<tr>
<td>ER physician fee</td>
<td>93 ± 29</td>
<td>98 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Drug</td>
<td>101 ± 57</td>
<td>5 ± 2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>402 ± 1920</td>
<td>1258 ± 1100</td>
<td>NS</td>
</tr>
<tr>
<td>Medical consult</td>
<td>148 ± 77</td>
<td>109 ± 27</td>
<td>NS</td>
</tr>
<tr>
<td>ICU consult</td>
<td>400 ± 71</td>
<td>276 ± 63</td>
<td>NS</td>
</tr>
<tr>
<td>ICU</td>
<td>327 ± 2410</td>
<td>1245 ± 490</td>
<td>b</td>
</tr>
<tr>
<td><strong>Total cost</strong></td>
<td><strong>1524 ± 2520</strong></td>
<td><strong>1432 ± 1420</strong></td>
<td>NS</td>
</tr>
</tbody>
</table>

Canadian dollar = 0.73 United States dollar; b sample size inadequate to compare costs."
Guidelines for routine flumazenil use

- 0.1 à 0.3 mg IV bolus
- Titration to avoid withdrawal syndrome
- More elevated dosage regimen if multi-drug poisoning: up to 2 mg bolus
- Efficient in poisonings with assimilated molecules (zopicolone and zolpidem)
- Caution if tricyclic antidepressants or carbamazepine co-ingestion
- Add bolus or continuous infusion (0.3-0.5 mg/h) to maintain consciousness
- Significant improvement in respiratory conditions to avoid tracheal intubation
- Debated utilization in ethanol poisoning or liver encephalopathy
- Efficient and safe utilization in elderly, children, babies, pregnant women

Flumazenil in children:
- 10-20 \( \mu g/kg \) IV bolus
- Experience (N=83; 2 years [3 months,12 yrs]): excellent tolerance, no convulsion

Weinbroum AA. Drug Safety 1997

Kreshak AA. Pediatr Emerg Care 2012
Antidote to treat acetaminophen poisoning
N-acetylcysteine

- N-acetylcysteine administration is indicated in severe acetaminophen poisonings (SID ≥ 125 mg/kg), assessed by the measurement of plasma concentration and its interpretation using Rumack & Matthew’s nomogram (zones of possible or probable toxicity).

- Protective effect is maximal if administered < 10h after ingestion.

Validity conditions
- Acute ingestion of an unique dose
- Known ingestion time
- Sampling > 4h post ingestion
- Specific assay

Expert recommendations, SRLF 2006
Risk of liver toxicity according to the different treatment lines of acetaminophen concentration.

The optimal equilibrium between the risks of persistent acetaminophen liver toxicity and onset of NAC side-effects.

Beer et al. QJM 2007
Death related to the non-administration of NAC based on the treatment lines

10 fatalities since 1992:
- 6 in 150-200 mg/l range
- 1 in 100-150 mg/l range
- 3 in < 100 mg/l

Reasons:
- Co-ingestions or SR formulation
- Extreme vulnerability
Modification of NAC treatment line to 100 mg/l in 2012 in the UK

100 mg/l

- patients treated with NAC, mainly in the 100 - 149 mg/L range (patients at mild risk of toxicity but higher risk of side-effects)

Bateman N. Clin Tox 2014
The very particular situation of Denmark

- All the patients admitted for acetaminophen poisoning are treated with NAC according to Prescott’s dose regimen

- Measurement of serum acetaminophen concentration is only used to assess the diagnosis of exposure

- The nomogram is never used

**Explanation:**
- The presumed ingested dose is not always reliable
- Bad prognosticators and vulnerability factors are usually unknown

**Overview:** Increased NAC side-effects and treatment costs
**Decision:** Modification of NAC dose regimen, STOP rules
Improving dose regimen to reduce NAC-related side effects

Prescott’s standard dose regimen:
150 mg/kg in 15 min; 50 mg/kg in 4 h; 100 mg/kg in 16 h (Total: 20 h)

Modified dose regimen:
100 mg/kg in 2 h; 200 mg/kg in 10 h (Total: 12 h)

With or without ondansetron pretreatment

Bateman N. Lancet 2013

No need of antiemetic treatment between 0-12h

No need of anti-allergic treatment between 0-12h
## Chronic intoxication with acetaminophen

<table>
<thead>
<tr>
<th></th>
<th>Voluntary</th>
<th>Accidental</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen dose</td>
<td>20g</td>
<td>12g</td>
<td>0.009</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>25%</td>
<td>63%</td>
<td>0.009</td>
</tr>
<tr>
<td>ALT &gt; 3,500 IU/L</td>
<td>14%</td>
<td>52%</td>
<td>0.002</td>
</tr>
<tr>
<td>Coma</td>
<td>6%</td>
<td>33%</td>
<td>0.006</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>2%</td>
<td>19%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Treat largely

Schiodt FV. NEJM 1997
Delayed presentation with liver failure

Retrospective study of 100 patients with liver failure

- Mortality in patients who received NAC >10 h: 37%
- Mortality in patients who did not receive NAC: 58%

Prospective randomized in 100 patients with liver failure

<table>
<thead>
<tr>
<th>Treatment with NAC</th>
<th>Survival</th>
<th>Brain edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC + (n=50 *)</td>
<td>48 %</td>
<td>40 %</td>
</tr>
<tr>
<td>NAC - (n=50)</td>
<td>20 %</td>
<td>68 %</td>
</tr>
</tbody>
</table>

* Mean delay: 53 h

Treat systematically

Harrison P. Lancet 1990
Keays R. BMJ 1991
Antidotes

to treat drug-related cardiovascular failure
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
Optimal supportive treatments in the 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, MgSO$_4$, titrated isoproterenol, cardiac pacing
  - Correction of electrolyte imbalance (K$^+$, Mg$^{2+}$)

- **Treatment of monomorphic ventricular tachycardia**
  - Defibrillation, MgSO$_4$, lidocaine infusion

- **Cardiac pacing**
  - High degree AV block with preserved inotropism
Sodium bicarbonates to treat membrane stabilizing effects

84‰ Sodium bicarbonate 250 ml + KCl 2g <750 ml, pH <7.55

Sasyniuk J. JPET 1984
Mechanism of the main antidotes to reverse cardiotoxicity

**Calcium salts**

**Beta-agonists**

**Glucagon**

**Insulin - Glucose**
Methylene blue to antagonize relaxation of vascular smooth muscle by NO - The NO-cGMP pathway -

Mechanisms of CCB-related vasodilatation
- Blockade of L-type calcium channels
- Phosphorylation and eNOS resulting in NO release

Optimal administration of antidotes in the poisonings with cardiotoxicants (1)

**Beta-blockers**
- **Dobutamine** 5-20 µg/kg/min
- **Isoprenaline** 1-5 mg/h (Sotalol)
- **Glucagon** 2-5 mg IV bolus
  2-10 mg/h continuous infusion
- **Epinephrine** 0.5-10 mg/h
  ± Cardiac Pacing

**Calcium channel blockers**
- **Calcium chloride** 1 g IV bolus /15 min 4 doses, 20-50 mg/kg/h infusion
- **Insulin** 1 IU/kg IV bolus
  1-10 IU/kg/h continuous infusion
- **Epinephrine** 0.5-10 mg/h
- **Norepinephrine** 0.5-10 mg/h
- **Methylene blue** 2 mg/kg bolus
  1 mg/kg/h infusion
Optimal administration of antidotes in the poisonings with cardiotoxicants (2)

**Sodium channel blockers**

- **Sodium bicarbonate** 8.4%
  - 250 ml to be repeated 3 times
  - + 2g KCl / 250 ml
    - (cocaine: **Lidocaine IV**)

- **Epinephrine** 0.5-10 mg/h
- **Norepinephrine** 0.5-10 mg/h

**Cardioglycosides**

- **Atropine** 0.5-1 mg to be repeated

- **Anti-digoxin Fab fragments**
  - Semi-molar or molar dose
  - (if not available: ventricular pacing)
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?

Finn SD. Anesthesia 2009
Weinberg GL. Anesthesiology 2009
Partition constant and volume of distribution as predictors of ILE efficacy for toxicological emergencies

Serum drug concentration decrease plotted against the partition constant and the volume of distribution of eleven drugs with 2% Intralipid® added to the sample.
Agents with positive bench evidence for class effect and reported clinical use associated with a positive outcome

<table>
<thead>
<tr>
<th><strong>Na(^+)-channel antagonists</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Local anesthetics</td>
<td></td>
</tr>
<tr>
<td>- Tricyclic antidepressants:</td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
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<tr>
<td>Amitryptilline</td>
<td></td>
</tr>
<tr>
<td>Dothiepin</td>
<td></td>
</tr>
<tr>
<td>- Flecainide</td>
<td>[bench model evidence equivocal]</td>
</tr>
<tr>
<td>- Propafenone</td>
<td></td>
</tr>
<tr>
<td>- Cocaine</td>
<td></td>
</tr>
<tr>
<td><strong>Ca(^{2+})-channel blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
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<tr>
<td>Carvedilol</td>
<td></td>
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<tr>
<td>Nebivolol</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
</tbody>
</table>
Lipid emulsion: state of the Art

While the evidence base for ILE use in drug intoxication is evolving, the present evidence supports its use only in local anesthetic systemic toxicity and lipophilic cardiotoxin intoxication when there is an immediate threat to life, and other therapies have proven ineffective.
**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 prognosticators**
- 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 anti-digoxin 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.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>(gender)</th>
<th>History</th>
<th>Other Toxins</th>
<th>Overdose</th>
<th>Glycoside</th>
<th>Serum Concentration (ng/mL)</th>
<th>K (mmol/L)</th>
<th>ECG</th>
<th>Fab Dose (vials)</th>
<th>Time Before Fab (hrs)</th>
<th>Time to Death (hrs)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>M</td>
<td>Cardiac failure</td>
<td>Verapamil</td>
<td>Voluntary</td>
<td>Digoxin</td>
<td>23.4</td>
<td>4.6</td>
<td>VF</td>
<td>12</td>
<td>?</td>
<td>&lt;1</td>
<td>Cardiac failure</td>
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<tr>
<td>90</td>
<td>F</td>
<td>Cardiac failure, diabetes</td>
<td>None</td>
<td>Treatment</td>
<td>Digoxin</td>
<td>7.5</td>
<td>4.6</td>
<td>AVB I</td>
<td>2</td>
<td>NA</td>
<td>72</td>
<td>MOF</td>
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<tr>
<td>82</td>
<td>M</td>
<td>Parkinson’s disease, cardiac failure</td>
<td>Meprobamate, TCA</td>
<td>Voluntary</td>
<td>Digitoxin</td>
<td>230.0</td>
<td>4.7</td>
<td>VF</td>
<td>12</td>
<td>10</td>
<td>60</td>
<td>MOF</td>
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<tr>
<td>71</td>
<td>M</td>
<td>Cancer</td>
<td>None</td>
<td>Treatment</td>
<td>Digoxin</td>
<td>7.3</td>
<td>5.7</td>
<td>VF</td>
<td>3</td>
<td>NA</td>
<td>36</td>
<td>MOF</td>
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<tr>
<td>82</td>
<td>F</td>
<td>Cardiac failure, AF, and HTA</td>
<td>Betablocker</td>
<td>Treatment</td>
<td>Digoxin</td>
<td>4.6</td>
<td>4.7</td>
<td>AF</td>
<td>2</td>
<td>3</td>
<td>19</td>
<td>MOF</td>
</tr>
</tbody>
</table>

Death: sepsis, co-ingestion, post-cardiac arrest anoxia

Lapostolle F. Crit Care Med 2009
Antidotes to treat toxic alcohol poisonings (metabolic acidosis)
Toxic alcohol poisonings

Alcohol: offending chemicals in suicide, unintentional and epidemic poisonings

- Ethylene glycol: 4867 exposures /year (mortality: 0.09%)
- Methanol: 2418 exposure/year (mortality: 0.05%)

Toxicity is due to enzymatic degradation by alcohol dehydrogenase

- Methanol: CH₃OH
  - ADH → Formaldehyde: HCHO
    - AIDH → Formate: HCOO⁻
    - Blindness
    - Metabolic acidosis
    - CO₂ + H₂O
    - Folate
  - ADH → Ethylene Glycol: CH₂OH - CH₂OH
    - ADH → Glyoxal: CH₂OH - CHO
      - AIDH → Glycolate: CH₂OH - COO⁻
        - AIDH → Oxalate: COO⁻ - COO⁻ + Ca²⁺
          - Metabolic acidosis
          - Coma + seizures
          - Renal failure
          - Myocarditis
Treatment of toxic alcohol poisonings

Recommended treatments include:

- Supportive treatments
- Sodium bicarbonate:
  - to correct metabolic acidosis
  - to increase renal elimination of glycolate and formate
  - to inhibit precipitation of calcium oxalate crystals
- Intermittent dialysis used routinely to correct acidosis, to remove toxic metabolites and to shorten the course of hospitalization (methanol)

+ Antidotes (competitive ADH inhibitor or substrate): fomepizole and ethanol

Jacobsen D. Clin Toxicol 1997
Brent J. NEJM 2009
Indications for the treatment of toxic alcohol poisoning with antidotes

Initial management is focused on preventing the development of metabolic acidosis, acute renal failure, ophthalmologic abnormalities, and coma if not already supervened, or correcting the acid-base disturbance if present

- Documented recent history of ingesting toxic amount of methanol/EG and osmolal gap > 10 mOsm/kg

- History or strong clinical suspicion of methanol/EG poisoning and at least 2 of the following criteria
  - Arterial pH < 7.3
  - Serum bicarbonate < 20 meq/L (mmol/L)
  - Osmolal gap > 10 mOsm/kg H₂O

- Documented plasma concentrations > 0.20 g/L
Assessment of fomepizole efficacy:

Half-lives in the presence of the antidote

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous</th>
<th>Ethanol</th>
<th>Fomepizole</th>
<th>Ethanol +</th>
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<tbody>
<tr>
<td><strong>Hemodialysis</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>2.5 - 4.5</td>
<td>17</td>
<td>20</td>
<td>2.6</td>
</tr>
<tr>
<td>Methanol</td>
<td>3.0</td>
<td>43</td>
<td>54</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Advantages of fomepizole over ethanol as antidote for suspected alcohol poisoning

Ease of administration
- Fixed loading dose independent of baseline concentration
- Intermittent bolus dosing /12 hours (/4 h during dialysis)

Absence of CNS depression and inebriation
Absence of metabolic and biochemical adverse effects

No need for monitoring serum antidote concentrations or continuous infusion
Ability to forgo hemodialysis in selected patients

Reduced intensity of nursing care
Simplification of interfacility transfer

Administer a loading dose in case of exposure to methanol or ethylene glycol or in the presence of anion gap acidosis if not explained by lactates

Sivilotti ML. Ann Emerg Med 2009
Antidotes to treat insecticide/pesticide poisonings (developing and rural countries)
Organophosphorous poisonings

> 3 000 000 severe poisonings /year; > 220 000 deaths /year
In Sri Lanka, deaths from OP poisonings > deaths from infectious diseases

At least 70 different marketed OPs including 5 majors (50% sales): methylparathion, parathion, terbufos, fonofos, and azynphos methyl

+ Chemical weapons (tabun, soman, sarin) used in Tokyo (subway attack) /Syria

**OP** = Irreversible inhibitors of cholinesterases
(acetylcholinesterase, butyrylcholinesterase, carboxylesterase)

→ Phosphorylation of AchE esterase active site
→ Accumulation of Ach in the cholinergic synapse

**Atropine** = 1st line antidote - efficient - Target = stop pulmonary secretions
**Oximes** = Activators of the spontaneous enzyme dephosphorylation before ageing (covalent binding)
Pralidoxime concentration/effect relationships in rat

\[ y = 4969.7 \ln(x) + 4265.6 \]

\[ R^2 = 0.9819 \]

Houzé P. Tox Sci 2011
PK/PD relationships regarding oxime efficacy in OP-poisoned rats

- Concentration = 7.1 mg.L⁻¹ in elimination phase = inefficiency
- Concentration = 7.3 mg.L⁻¹ in resorption phase = efficiency

Houzé P. Tox Sci 2011
Treatment with oxime is not associated with a decrease in the mortality rate.
Treatment with oxime is not associated with a decrease in mechanical ventilation
Treatment with oxime is not associated with a reduction in the intermediate syndrome incidence
Usefulness of pralidoxime in organophosphorous poisonings

- Pralidoxime is an efficient AChE reactivator, however, concerns regarding its utility and safety are still raised.

- The adequate pralidoxime dose regimen, its aimed plasma concentration as well as the subgroup of patients that may benefit are unknown.

Eddleston M. Lancet 2005
Eddleston M. PLoS  2009
Role of an elevated dosage regimen of pralidoxime in organophosphorous poisonings

Study group: 2 g loading dose over 30 min then 1 g over 1 h /1 h for 48 h.
Control group: 2 g loading dose over 30 min then 1 g over 1 h /4 h for 48 h.

Pawar KS. Lancet 2006

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Control group (n=100)</th>
<th>Study group (n=100)</th>
<th>Difference or relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days ventilated</td>
<td>10 (8-12)*</td>
<td>5 (4-5)†</td>
<td>5 (5-6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median atropine dose in first 24 h (mg)</td>
<td>30 (25-45)</td>
<td>6 (4-6)</td>
<td>24 (24-26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neck muscle weakness</td>
<td>94 (94%)</td>
<td>80 (80%)</td>
<td>0.85 (0.76-0.95)†</td>
<td>0.0054‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.65-0.98)$</td>
<td>0.00545</td>
</tr>
<tr>
<td>Intubated during admission</td>
<td>88 (88%)</td>
<td>64 (64%)</td>
<td>0.72 (0.62-0.86)§</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intubated after randomisation</td>
<td>19/31 (61.3%)</td>
<td>1/37 (2.7%)</td>
<td>0.044 (0.063-0.31)‡</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.045 (0.005-0.31)$</td>
<td>0.00015</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>8 (8%)</td>
<td>1 (1%)</td>
<td>0.13 (0.016-0.98)†</td>
<td>0.0349‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.11 (0.01-0.84)$§</td>
<td>0.00350§</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>35 (35%)</td>
<td>8 (8%)</td>
<td>0.23 (0.11-0.47)†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.23 (0.10-0.47)$§</td>
<td>&lt;0.0015</td>
</tr>
<tr>
<td>Mean systolic blood pressure in first 24 h (mm Hg)</td>
<td>115.4 (6-10)$</td>
<td>136.2 (4.97)‡</td>
<td>20.6 (19-0.22.2)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mean diastolic blood pressure in first 24 h (mm Hg)</td>
<td>75.6 (4.96)§</td>
<td>84.1 (2.56)‡</td>
<td>8.3 (7.2-9.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*n=80, †n=63, ‡Unadjusted values, §Adjusted values, ¶n=97, ‖n=99.
Why it is difficult to prove pralidoxime usefulness in OP poisoning?

• Different OPs with various ingested doses (known in 18%).
  Kinetics of AchE ageing and reactivation depends on the OP.
• Variable pralidoxime doses.
• Variable delays to pralidoxime administration.
• Pralidoxime side-effects: respiratory depression, liver toxicity, dysrrhythmia, ...

Stratified controlled randomized trials with
Classify poisonings according to OP (diethyl- vs. dimethyl-)
Monitor pralidoxime concentration
Determine the delay between OP ingestion and treatment
Antidotes to treat cyanide poisoning (smoke inhalation)
Cyanide poisoning: a large spectrum

Sometimes, diagnosis is evident:

- **Industrial incidents**: fumigation, chemicals, metallurgy, organic synthesis, ...
- **Individual suicide attempt** (chemists or engineers)
- **Therapeutic exposure** to nitroprussiate

In other conditions, diagnosis is not evident:

- **Individual suicide attempt** with an unknown compound
- **Terrorist attack**
- **Smoke inhalation** in residential fires
- **Poisonings with nitriles**

**Dietary exposure** to cyanogenic plants (cassava) CN poisoning is rare but responsible of severe injuries. Recognition of a non-classical situation of CN poisoning may be difficult. Laboratory diagnosis may take hours to days. Early aggressive treatment with appropriate antidotes is essential
When to suspect cyanide poisoning in smoke inhalation?

**Neurological**
- Dizziness
- Restlessness
- Anxiety
- Confusion
- Coma
- Seizures

**Respiratory**
- Hyperpnea
- Central apnea
- \( \pm \) Pulmonary edema

**Cardiovascular**
- Hypertension
- Shock
- Cardiac arrest

**Metabolic**
- Blood glucose
- Lactate
- Metabolic acidosis
- Rhabdomyolysis
- Renal failure

- Abnormal respiratory pattern
- Abnormal arterial pressure
- Lactates \( > 10 \text{ mmol/l} \)

\( CO \) and \( CN \)
Hydroxocobalamin (Cyanokit®)

- Currently used in Europe and more recently in the USA
- 50 g bind 1 g of CN
- Dose: 5 g, to be repeated according to seriousness.
- Ability to pass through the BBB
- Side-effects: reddish discoloration of skin and urine, allergic reactions

First-line antidote

Other CN antidotes

Sodium thiosulfate:
- efficient - safe
- delayed action

MetHb forming agents:
- potent
- impairment of O₂ delivery

Cobalt EDTA:
- very potent
- immediate action
- effective if late
- numerous side effects
**EuSEM guidelines 2012**

**Pre-hospital algorithm**

- **Smoke inhalation incident**
  - Evaluate:
    - Fire in an enclosed space
    - Duration of exposure
    - Number of victims

- **Administer O₂ 100%**
  - Severe poisoning: GCS ≤ 9
  - Intermediate poisoning: GCS 10–13 and/or abnormal ABC
  - No neurological and/or hemodynamic symptoms: GCS ≥14

- **Collect blood samples, if possible**

- **Transfer to hospital**

  - Hydroxocobalamin 5 g (70 mg/kg)*
  - Hydroxocobalamin 5 g (70 mg/kg)**
  - Monitoring
Hospital algorithm

**EuSEM guidelines 2012**

Smoke inhalation incident

- Basic effects of smoke
- Other injuries (burns, trauma, ...)
- Refer to other protocols

Administer O₂ 100%

- History (type of fire, duration of exposure)
- Clinical examination
- Technical examination – imaging:
  1. Lactates
  2. HbCO
  3. Arterial and venous blood gas
  4. Laboratory as needed
  5. ECG
  6. Thorax X-rays (only if necessary)
  7. CN analysis (not required for acute treatment)

Co poisoning

Treat if clinical sings or HbCO > 10%

Follow local guidelines

Need for end organ monitoring

Consider Sodium thiosulfate

Cyanide poisoning

- Pre-hospital antidote
- Lactate **
- HOCO* 5g (70 mg/kg) IV
- Lactate after 2h
- Consider discharge

- No antidote
- Lactate **
- HOCO* 5g (70 mg/kg) IV
- Lactate after 2h
- Consider discharge
Potential interference by hydroxocobalamin on cooximetry hemoglobin measurements

Blood leak alarm interference by hydroxocobalamin is hemodialysis machine dependent

<table>
<thead>
<tr>
<th>Dialysis machine</th>
<th>Manufacturer</th>
<th>Is Pseudo-blood leak likely to happen with hydroxocobalamin use?</th>
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<td>Althin</td>
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<tr>
<td>C3</td>
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<td>DBB 06</td>
<td>Nikkiso</td>
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<td>DCS-6</td>
<td>Nipro</td>
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<td>Dialog Plus</td>
<td>B-Braun</td>
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<td>Diapact</td>
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<td>Diamax</td>
<td>Nipro</td>
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<td>Formula 2000 Plus</td>
<td>Bellco</td>
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<tr>
<td>Prismaflex</td>
<td>Gambro</td>
<td>No</td>
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</tbody>
</table>

Sutter ME. Clin Tox 2012
Avila J. Clin Nephrol 2012
Two poisons with still no efficient antidote

Colchicine poisoning
Paraquat poisoning
Immunotoxicootherapy to treat colchicine poisoning
Hopeful pulse immunosuppressive therapy to treat paraquat poisoning

Prospective randomized trial (N = 50)

- Cyclophosphamide: 15 mg/kg on D1, D2
- Methylprednisolone: 1 g on D1, D2, D3
- Dexamethasone: 10 mg / 8 h 14 days

+ Charcoal, emergent hemoperfusion (2 x 8 h)

Benefit in minor/moderate poisonings (excluding patients who died from multiorgan failure before 7 days) [death: 18% vs 57%, p=0.005]

However: Diagnosis based on dithionate coloration of the urine
No measurement of serum paraquat

Lin JL. Am J Respir Crit Care Med 1999
Lin JL. Crit Care Med 2006
General principles to use antidotes in practice

1- The antidote should be used once the supportive treatments have been performed in life-threatening presentations.

2- The antidote may be used as pharmacodynamic test to reverse coma or respiratory depression (naloxone, flumazenil).

3- Antidote use is mandatory with toxicants at risk of organ injuries (acetaminophen).

4- Antidote may optimize the functional prognosis in association with efficient supportive cares.

5- Antidote use should take into account its side-effects and the reversal of any possible toxicant-related protective effect.
Conclusions (2)

For the future

- There is a need for RCT in clinical toxicology to improve practice.

- The interest of an antidote should be evaluated based on its expected benefits, adverse events, and cost.

- Its optimal administration modalities should result from evidence-based bench-to-bedside assessment.