Antidotes in acute intoxications
Antidotes: warnings

Antidotes are only one aspect of treatment

In case of uncommon antidotes: seek expert advice

These slides only discuss the general principles, not the precise indications, dosing strategies, ...
Examples of antidotes used in acute intoxications

<table>
<thead>
<tr>
<th>Antidotes</th>
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<tbody>
<tr>
<td>Naloxone</td>
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<tr>
<td>Flumazenil</td>
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<tr>
<td>N-acetylcysteine</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Glucagon</td>
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<tr>
<td>Sodium bicarbonate</td>
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<tr>
<td>Digoxin-specific antibody</td>
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<tr>
<td>Ethanol / fomepizole</td>
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<tr>
<td>Atropine and pralidoxime</td>
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<tr>
<td>Others: hydroxocobolamine, chelators...</td>
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</tbody>
</table>

Case #1

- 23-year-old man found comatose in a park
- Emergency medical services’ findings at the scene
  - **A** obstructive airway
  - **B** cyanosis, respirations 2 breaths/min
    ⇒ Head tilt, chin lift, oxygen, bag-valve-mask ventilation
  - **C** pulse 110 beats/min
  - **D** GCS 3/15, miotic pupils, no evidence of trauma
    glucose stick 108 mg/dl
  - **E** needle tracks
    ⇒ Naloxone IV for presumed opioid overdose after which the patient became alert with a respiratory rate of 22 breaths/min
Naloxone (Narcan®)

Opioid receptor antagonist:
  greater affinity for µ- than for κ-, δ-receptor
Pure: no depressant activity
Treatment of respiratory depression
Specificity: ethanol? clonidine? valproic acid?
Competitive, i.e. dose in function of the size of the ingested dose of agonist
Naloxone

Indications

- Coma and/or respiratory depression in patients manifesting opioid toxicity
  → adequate airway reflexes and ventilation

Adverse effects

- Potentially severe: withdrawal, acute pulmonary edema, hypertension, cardiac dysrhythmias
- Relatively uncommon when used in low doses and titrated to effect
- Resedation
Case #2

- 30-year-old woman
- Witnessed auto-intoxication
- 5 hours later: arrival at the emergency department
  - No information about ingested pills
  - **A** free airway
  - **B** respirations 18 breaths/min, pulse oximetry 99 %
  - **C** pulse 90 beats/min, blood pressure 120/75 mmHg
  - **D** GCS 10/15, pupils normal, no trauma
    bedside glucose stick 95 mg/dl
  - **E** temperature 37.0 °C
  - Electrocardiogram: sinus rhythm
  - Capillary blood gas analysis: pH 7.42, pCO₂ 36 mmHg, pO₂ 64 mmHg
  - Lab: normal
  - Toxicological analysis: ethanol -, salicylates -, acetaminophen 300 µg/ml
- After regaining consciousness, she admitted having taken lorazepam (about 40 mg) and acetaminophen (about 15 g)
GABA-NEURON

Cl⁻

GABA

BR

GABA-R.

EFFECTOR-NEURON

Benzodiazepine receptor antagonist: flumazenil (Anexate®)

Contra
- Morbidity and mortality are rare
- Aspiration pneumonitis prior to hospital admission
- Potential complications (e.g. convulsions) caused by:
  - Mixed overdose (e.g. tricyclic antidepressants)
  - Acute withdrawal
- >> No role in intoxications with unknown substances!

Pro
- No need for further diagnostic procedures in coma
- No need for endotracheal intubation en ventilation

Flumazenil: contraindications

Prior seizure history or current treatment of seizures
History of ingestion of a xenobiotic capable of provoking seizures or cardiac dysrhythmias
Long-term use of benzodiazepines
ECG evidence of cyclic antidepressants
Abnormal vital signs; hypoxia
Flumazenil: indications in overdose

Pure benzodiazepine overdose in a nontolerant individual who has

- CNS depression
- Normal vital signs including SaO2
- Normal ECG
- Otherwise normal neurologic examination
N-acetylcysteïne (NAC) (Lysomucil®)

Intoxications

- Paracetamol (= acetaminophen)
- other intoxications leading to glutathione depletion
e.g. carbon tetrachloride, chloroform

Fulminant hepatic failure
Figure 1. Acetaminophen Metabolism

Used with permission. Adapted from Black M. Acetaminophen hepatotoxicity. Gastroenterology 1980;78:385.
Paracetamol intoxication

<table>
<thead>
<tr>
<th>Stage 1 (30min – 24h): absence of hepatic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>• nonspecific clinical findings like nausea, vomiting, malaise, pallor</td>
</tr>
<tr>
<td>• may be asymptomatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2 (24h – 72h): onset of hepatic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>• increased liver enzymes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3 (72h – 96h): maximal hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• increased liver enzymes</td>
</tr>
<tr>
<td>• prolonged prothrombin time</td>
</tr>
<tr>
<td>• elevated bilirubin</td>
</tr>
<tr>
<td>• hypoglycemia</td>
</tr>
<tr>
<td>• metabolic acidosis</td>
</tr>
<tr>
<td>• hepatic encephalopathy</td>
</tr>
<tr>
<td>• renal dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4 (4 d - 2 w): recovery phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>• in case of survival: complete recovery</td>
</tr>
</tbody>
</table>
Paracetamol intoxication: Indications for N-acetylcysteine

A. Acute overdose

- Nomogram - ‘pitfalls’:
  - units
  - protracted ingestion
  - measurement < 4 h following ingestion
  - time of ingestion not exactly known
  - Lower treatment threshold in risk groups: CYP450 inducing substances, chronic ethanol use, starvation

- If $\geq 150$ mg/kg acetaminophen and concentration cannot be obtained within 8 h of the overdose
Paracetamol intoxication:
Indications for N-acetylcysteine

B. Chronic overdose

› Do not use nomogram!
› Decision for NAC based on history, physical examination, predisposing risk factors, liver enzymes, plasma concentrations
Paracetamol intoxication: N-acetylcysteine

**Timing**
- Most efficient when initiated within 8 h of an acute overdose
- Also useful when initiated later

**Route of administration:** intravenously

**Duration of treatment**
- 20-hour protocol
- Prolonged treatment if evidence of liver injury or incomplete acetaminophen metabolism
Paracetamol intoxication: N-acetylcysteine

Adverse effects

- Anaphylactoid reactions related to high serum NAC concentrations (only after i.v. administration)
- Elevated prothrombin time
- Iatrogenic overdoses

PS: Pregnancy is no contraindication
Case #3

- 52-year-old man found comatose in bed by his family
- Mobile intensive care units findings at the scene
  - A no free airway
  - B respirations 10 breaths/min, pulse oximetry 89 %
  - C pulse 38 beats/min, blood pressure 80/40 mmHg
  - D GCS 5/15, pupils normal, no evidence of trauma
    bedside glucose stick 80 mg/dl
  - E cool skin, no empty pill boxes
    ⇒ intubation, 1 mg atropine, 500 mL bolus saline
- Emergency department
  - Seizures
    ⇒ Diazepam 10 mg IV
  - Interview of the family: patient suffered from depression with suicidal thoughts, he stopped taking antidepressants one month ago and currently only takes antihypertensive medication
Case #3 (cont.)

- **Emergency department**
  - Electrocardiogram: sinus bradycardia with PR interval of 280 msec and a QRS duration of 140 msec
  - Deterioration of vital signs: systolic blood pressure 60 mmHg, pulse 28 beats/min
    → 1 mg atropine IV, colloids IV, external cardiac pacing, epinephrine IV
    → 100 meq sodium bicarbonate IV for presumed TCA poisoning
    → GI decontamination
  - No change in blood pressure, paced rhythm (60/min)
    → 1 g calcium chloride IV for presumed calcium channel blocker overdose
  - Systolic blood pressure 75 mmHg, pulse 35/min
Case #3 (cont.)

• Emergency department
  ▶ Additional information from family physician: prescription for bisoprolol 2 weeks earlier
  ▶ empty bisoprolol box found by family
    ⇒ 5 mg glucagon IV over 10 min followed by continuous infusion
  ▶ Blood pressure 105/60 mmHg, pulse 55 beats/min
  ▶ Lab: normal
  ▶ Arterial blood gas: mild anion gap metabolic acidosis
  ▶ Toxicological analysis: acetaminophen -, salicylates -, TCA –

• Uneventful recovery
Management of β-adrenergic antagonist and calcium channel blocker overdose

Adapted from Ann Pharmacother 2005; 39:923-930
Calcium as antidote: indications

Intoxication with calcium channel blockers
Intoxication with β-adrenergic antagonists
Ethylene glycol poisoning with hypocalcemia
Burns/intoxication with hydrofluoric acid
Hypermagnesemia
Hyperkalemia
(NOT in cardiac glycoside poisoning!)
Glucagon

Positive chronotropic and inotropic action related to an increase in cardiac cAMP levels (independent of $\beta$-receptor)

Indication

- Hemodynamic problems (hypotension, bradycardia) in overdoses with $\beta$-adrenergic antagonists and calcium channel blocker overdose
Glucagon

Adverse effects

- Nausea, vomiting (cave aspiration)
- Hyperglycemia
- Hypokalemia
- Rarely allergic reaction
- Insulinoma, pheochromocytoma
High-Dose Insulin Therapy for Calcium-Channel Blocker Overdose

Greene Shepherd and Wendy Klein-Schwartz

CONCLUSIONS: Based on animal data and limited human experience, as well as the inadequacies of available alternatives for patients with significant poisoning, high-dose insulin therapy warrants further study and judicious use in patients with life-threatening CCB poisoning.

Ann Pharmacother 2005; 39:923-930
Sodium bicarbonate in toxicology: mechanisms

Altered drug ionization and interaction with sodium channel:
  e.g. tricyclic antidepressants, antidysrhythmics (IA, IC), amantadine, phenothiazines

Enhancing elimination:
  e.g. salicylates, chlorophenoxy herbicides, phenobarbital

Correcting metabolic acidosis:
  e.g. toxic alcohols
Case #4

- 79-year-old woman
- Past history: congestive heart failure, hypertension
- Medication: digoxin, furosemide, aspirin
- Current history: nausea, weakness, vertigo
- Vital signs:
  - blood pressure 90/45 mmHg
  - pulse 35 beats/min
  - respiratory rate 16 breaths/min,
  - rectal temperature 37.1°C
- Electrocardiogram: high-degree heart block with ventricular escape rhythm of 30-35/min
- Treatment: atropine IV (no effect), transcutaneous pacing standby
- Digoxin concentration 3.8 ng/ml ⇒ digoxin-specific Fab IV

# Papain Digestion of IgG Antibody

<table>
<thead>
<tr>
<th>Type</th>
<th>Dipeptidyl Peptidase Site</th>
<th>Molecular Weight</th>
<th>Urinary Excretion</th>
<th>Serum half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG antibody</td>
<td>2 per molecule</td>
<td>160,000</td>
<td>No</td>
<td>23 days</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Type</th>
<th>Dipeptidyl Peptidase Site</th>
<th>Molecular Weight</th>
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<th>Serum half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fab fragments of IgG</td>
<td>1 per fragment</td>
<td>90,000</td>
<td>Yes</td>
<td>4.3 hours**</td>
</tr>
</tbody>
</table>

*Ratio of human IgG in man: **Ratio of rabbit Fab in rabbit

Butler et al., 1973
Digitalis intoxication: Fab Fragments

Cleavage of IgG (without Fc)

Highly efficient

Intravascular and interstitial binding followed by renal elimination

Adverse effects

- Very safe
- Hypokalemia
- Worsening of heart function
- Rapid ventricular rate
- Rarely allergic reactions
Digitalis intoxication:
Indications for Fab Fragments

- Any potential cardioactive steroid-related life-threatening dysrhythmia
- Potassium concentration > 5 mEq/L in setting of acute cardioactive steroid poisoning
- Chronic cardioactive steroid poisoning with dysrhythmias, significant gastrointestinal symptoms, or acute onset of significantly altered mental status, or renal insufficiency
- Serum digoxin concentration ≥ 15 ng/mL at any time, or ≥ 10 ng/mL 6 h postingestion (lower threshold in elderly)
- Ingestion of 10 mg in adult or 4 mg in child
- Prior to calcium use in a patient with characteristics suggestive of poisoning by a cardioactive steroid, a calcium channel blocker or a β-adrenergic antagonist
Case #5

- 28-year-old man
- Found comatose by his family with an empty can of methanol next to him, current history of depression

Vital signs
- **A** free airway
- **B** respirations 15 breaths/min, pulse oximetry 99% (on room air)
- **C** pulse 68 beats/min, blood pressure 99/56 mmHg
- **D** GCS 9/15, pupils normal, no evidence of trauma
  - bedside glucose stick 114 mg/dl
- **E** temperature 36.1 °C

- Electrocardiogram: sinus rhythm
- Arterial blood gas analysis: pH 7.36, pCO₂ 31 mmHg, pO₂ 94 mmHg
- Lab: lactate normal, HCO₃⁻ 16 meq/L, ethanol - measured osmolality 421 mOsm/kg
- Anion gap 18 mEq/L, osmolal gap 129 mOsm/kg
- Toxicological analysis: ethanol -, salicylates -, acetaminophen -
  - methanol 95 mg/dl, ethylene glycol -
- Treatment with fomepizole, leucovorin and hemodialysis
- Uneventful recovery

Toxic alcohols: treatment

Alcohol dehydrogenase inhibition

- Ethanol or fomepizole
- Prevents metabolism to toxic products
- No effect on toxic metabolites
## Fomepizole

<table>
<thead>
<tr>
<th><strong>Pro</strong></th>
<th><strong>Ease of use</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No need for concentration monitoring</td>
</tr>
<tr>
<td></td>
<td>No CNS depression</td>
</tr>
<tr>
<td></td>
<td>No hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>May avoid hemodialysis and ICU monitoring (?)</td>
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<table>
<thead>
<tr>
<th><strong>Contra</strong></th>
<th><strong>High cost</strong></th>
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<tbody>
<tr>
<td></td>
<td>No long term experience</td>
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</table>
Toxic alcohols:
Indications for antidote treatment

Documented plasma concentration > 20 mg/dL
Or
Documented recent history of ingesting toxic amounts and osmolal gap > 10 mOsm/kg H₂O
Or
History or strong clinical suspicion of toxic alcohol poisoning and at least two of the following criteria
  ▶ Arterial pH < 7.3
  ▶ Serum bicarbonate < 20 meq/L
  ▶ Osmolal gap > 10 mOsm/kg H₂O
  ▶ Urinary oxalate crystals present (in case of ethylene glycol)
Case #6

- 46-year-old suicidal farmer
- Brought to ED because of confusion and shortness of breath

**Vital signs**
- A hypersalivation
- B respirations 28 breaths/min, bronchorrhea, pulse oximetry 89 %
- C pulse 112 beats/min, blood pressure 180/110 mmHg
- D GCS 12/15, pupils normal, no trauma
  - bedside glucose stick 126 mg/dl
- E temperature 37.0 °C

**Additional clinical findings**
- Crackles in all lung fields, diaphoresis, copious vomiting, diarrhea and urination, fasciculations

**Cholinergic toxidrome**

**Management**
- Intubation
- Gastric lavage and activated charcoal
- Atropine and pralidoxime

AUTONOMIC NERVOUS SYSTEM

Parasympathetic

ACh

Pupil constriction
Bradycardia
Exocrine secretion
GI smooth muscle contraction
Bronchoconstriction

ACh

Diaphoresis

Sympathetic

ACh

ACh

ACh

Epi

Pupil dilatation
Tachycardia
Hypertension
Bronchodilation

Neuromuscular junction

Somatic

ACh

Fasciculation
Muscle weakness

CNS

ACH

Excitability
Lethargy
Confusion
Coma
Seizure
Death

CENTRAL NERVOUS SYSTEM

Neurotransmission
Cholinesterase inhibitors

Organic phosphorus compounds

Carbamates

- Less CNS effects
- Shorter acting: reversible carbamate-cholinesterase bond
Cholinesterase inhibitors: Atropine antidote

Antagonizes ACh at muscarinic receptors to reverse excessive secretions, miosis, bronchospasm, vomiting, diarrhea, diaphoresis, urinary incontinence, bradycardia and CNS symptoms

No reversal of nicotinic effects
Cholinesterase inhibitors:
Oxime antidote

Pralidoxime (Contrathion®)
Reactivates AChE, inactivates free organic phosphorus molecules, exhibits antimuscarinic effect on nervous tissue
Most important at nicotinic receptors (muscle strength)
Always in combination with atropine