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Poisons and Poisoning

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Poisons and Poisoning

φαρμακον
pharmakon

Medicine Poison Magic Spell

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Objectives

- Appreciate the difference between acute overdose and chronic exposure
- Learn some typical signs of drug poisoning
- Understand the pharmacological basis for enhancing elimination of drugs
- Understand the pharmacological basis for the use of specific antidotes

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Poisoning

- Types
 - » Acute Overdose
 - » Chronic Exposure

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Diagnosis

- History
 - » Patients rarely lie
 - » But may be unreliable
 - Sedation
 - Amnesic drug effects

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Diagnosis

- Pupils
 - » Constricted
 - opiates (morphine)
 - clonidine
 - anti-cholinesterases (neostigmine)
 - » Dilated
 - atropine
 - tricyclic antidepressants (amitriptyline)
 - amphetamine/MDMA ('ecstasy')/BZP ('party pills')

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MDMA 3,4-Methylenedioxymethamphetamine
<http://en.wikipedia.org/wiki/MDMA>
BZP benzylpiperazine
<http://en.wikipedia.org/wiki/Benzylpiperazine>

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Diagnosis

- Skin
 - » Sweating
 - Increased amphetamine
 - Decreased atropine

 - » Bullae
 - carbon monoxide
 - [barbiturates]

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Diagnosis

- Odour
 - » ethanol
 - » garlic
 - arsenic
 - organophosphates
(anti-cholinesterase)
 - » almonds
 - cyanide

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Diagnosis

- Clinical Chemistry
 - » Blood
 - salicylate
 - paracetamol
 - ethanol
 - carbon monoxide
 - tricyclics
 - digoxin
 - theophylline

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Diagnosis

- Clinical Chemistry
 - » Urine
 - salicylate
 - opioids
 - tricyclics

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Diagnosis

- ECG
 - » Long PR – Calcium Channel
 - Verapamil
 - » Wide QRS – Sodium Channel
 - Amitriptyline
 - » Long QT – Potassium Channel
 - Amiodarone

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Treatment

- General Supportive
 - » A Airway
 - » B Breathing
 - » C Circulation

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Decrease Absorption

- emesis
 - » syrup of ipecac
- gastric lavage
 - » must have reflexes
 - » not for corrosives/hydrocarbons
- activated charcoal - **IMPORTANT**
 - » 50g every 4 h
- Fuller's Earth (or activated charcoal)
 - » Paraquat (herbicide)



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http://en.wikipedia.org/wiki/Activated_charcoal
http://en.wikipedia.org/wiki/Fuller's_earth

Note that treatment of paraquat poisoning seems to be rarely effective.
Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5):745-57.

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Increase Elimination

- Activated Charcoal
 - » "enteral dialysis"
- Haemoperfusion
 - » charcoal theophylline
 - » ion exchange salicylate
- Haemodialysis
 - » methanol (wood alcohol)
 - » ethylene glycol (anti-freeze)
- [Diuresis]

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Specific Antidote

- N-acetylcysteine
 - » paracetamol
- Naloxone
 - » morphine
- Flumazenil
 - » benzodiazepines
- Ethanol
 - » methanol

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Specific Antidote

- Chelation
 - » Desferrioxamine iron
 - » Succimer lead
 - » D-Penicillamine copper, mercury
 - » Hydroxycobalamin cyanide
- Atropine/pralidoxime
 - » anti-cholinesterases
- Antibody
 - » Fab fragments digoxin
 - » idarucizumab dabigatran
 - » andexanet rivaroxaban/apixaban

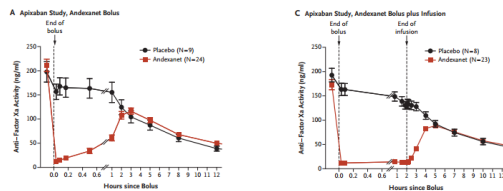
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Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med*. 2015 DOI: 10.1056/NEJMoa1502000

Eddleston M, Chowdhury FR. Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. *Br J Clin Pharmacol*. 2015;doi:10.1111/bcp.12784.

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Anti Factor Xa Activity



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Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med*. 2015;doi:10.1056/NEJMoa1510991.

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Specific Antidote

- Paracetamol Hepatotoxicity
 - » Minor metabolite is NAPQI (N-acetyl-p-benzoquinoneimine)
 - Formed by CYP2E1
 - Ethanol induces CYP2E1
 - » NAPQI inactivated by glutathione
 - » Liver damage caused by NAPQI
 - » Glutathione reserves used up by large doses (> 15 grams of paracetamol)
- Acetylcysteine supplies SH to make more glutathione
- UK guidelines (2014) for treatment shown to be cost-ineffective

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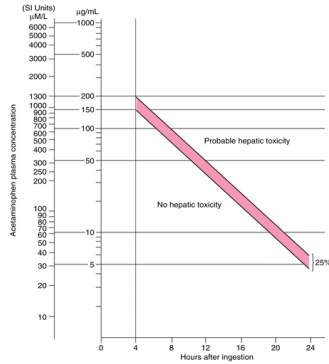
“Paracetamol poisoning is the most common acute overdose seen in industrialized countries [1, 2]. It is estimated that between 82 000 and 90 000 patients present in the UK each year with paracetamol overdose [3–5]. Between 150 and 250 deaths occur annually, the vast majority in patients who have presented late, after a staggered overdose or after unintentional therapeutic excess [6–9]. Deaths or episodes of liver failure in patients [10] who present and are treated within 8 h of a single acute ingestion are extremely rare [1, 5, 11].”

Bateman DN, Carroll R, Pettie J, Yamamoto T, Elamin MEMO, Peart L, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. *Br J Clin Pharmacol*. 2014;78(3):610-8.

A “two bag” 12 h administration of acetylcysteine appears to be safer. Chiew AL, Isbister GK, Duffull SB, Buckley NA. Evidence for the changing regimens of acetylcysteine. *Br J Clin Pharmacol*. 2016;81(3):471-81.

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N-Acetylcysteine Treatment Nomogram for Paracetamol Overdose in Adults



Children:
225 mg/L at 2 hours
Anderson et al. 1999
[Auckland]

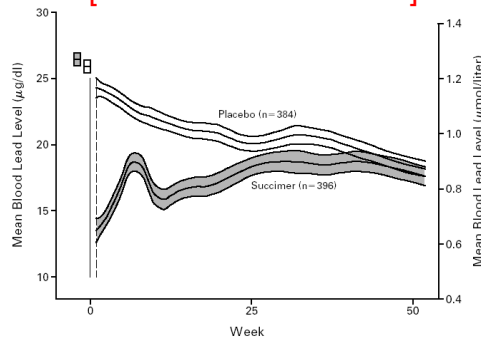
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<http://www.merck.com/mmpe/sec21/ch326/ch326c.html>

Anderson BJ, Holford NH, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. J Pediatrics. 1999;135(3):290-5.

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Specific Antidote [...but no effect on NPD]



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NPD=NeuroPsychological Development
TREATMENT OF LEAD EXPOSED CHILDREN TRIAL GROUP THE EFFECT OF CHELATION THERAPY WITH SUCCIMER ON NEUROPSYCHOLOGICAL DEVELOPMENT IN CHILDREN EXPOSED TO LEAD N Engl J Med 2001;344:1421-6

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Clinical Applications

- Approach to Poisonings
 - » ABC and General Support
 - » Specific antidotes are uncommon
- Use physiology and pharmacology to assist in diagnosis
- Consider factors affecting drug clearance if enhanced elimination procedures are used

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