Poisons and Poisoning

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

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Greek: φαρμακον

pharmakon

Medicine  Poison  Magic Spell

Objectives

➢ Learn some typical signs of acute drug poisoning
➢ Understand the pharmacological basis for enhancing elimination of drugs
➢ Understand the pharmacological basis for the use of specific antidotes

Diagnosis

➢ History

» Patients rarely lie

» But may be unreliable
   – Sedation
   – Amnesic drug effects

Diagnosis

➢ Pupils

» Constricted
   – opiates (morphine)
   – clonidine
   – anti-cholinesterases (neostigmine)

» Dilated
   – atropine
   – tricyclic antidepressants (amitriptyline)
   – amphetamine/MDMA (‘ecstasy’) / BZP (‘party pills’)

Diagnosis

➢ Skin

» Sweating
   – Increased amphetamine
   – Decreased atropine

» Bullae
   – carbon monoxide
   – [barbiturates]
Diagnosis

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

Diagnosis

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

Diagnosis

➢ Clinical Chemistry
  » Urine
    – salicylate
    – opioids
    – tricyclics
Diagnosis

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

Treatment

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

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)

Treatment of corrosive ingestion is reviewed here:

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.
Increase Elimination

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

[Diuresis]

Note also fomepizole may be used to treat ethylene glycol and methanol poisoning (https://en.wikipedia.org/wiki/Fomepizole)

Specific Antidotes

- **N-acetylcysteine**
  - paracetamol
- **Naloxone**
  - morphine
- **Flumazenil**
  - benzodiazepines
- **Ethanol**
  - methanol
- **Fomepizole**
  - ethylene glycol, methanol

Naloxone is licensed in NZ as a nasal spray https://nzf.org.nz/nzf_7017. This formulation is intended for emergency use by non-health professionals but is currently only available on prescription. Naloxone is available in the USA for over the counter sale from pharmacies (Cohen et al 2020).


Anti Factor Xa Activity


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

Ethanol can induce and “block” CYP2E1 at the same time. The “blocking” of metabolism of ethanol by itself is a manifestation of mixed-order saturable elimination as shown by the associated decrease in ‘clearance’ due to concentration dependent clearance. There are four processes involved in the paracetamol and ethanol interaction which are based on the same underlying mechanism of binding to CYP2E1.

1. Metabolism of ethanol by CYP2E1
2. Induction of CYP2E1 by ethanol
3. Metabolism of paracetamol by CYP2E1
4. Inhibition of paracetamol CYP2E1 metabolism by ethanol

When ethanol binds to CYP2E1 it is metabolized and with continued ethanol binding the CYP2E1 protein is induced so that the enzyme becomes more active and metabolism is faster. When paracetamol binds to CYP2E1 it is metabolized to NAPQI. If ethanol is present and bound to CYP2E1 then paracetamol metabolism to NAPQI is reduced because of competition for the same binding site.

The process of induction and de-induction is gradual with a protein turnover half-life of about 3 days so it takes about 2 weeks to induce and 2 weeks to de-induce. When ethanol binding is no longer present then the CYP2E1 protein decreases (de-induction) and enzyme activity returns to the uninhibited state.

If CYP2E1 has been induced and ethanol is stopped (and therefore not bound to CYP2E1) then paracetamol will be metabolized more quickly to NAPQI. As CYP2E1 becomes de-induced the metabolism of paracetamol will decrease until activity returns to the uninhibited state.

The risk of hepatotoxicity from paracetamol metabolism to NAPQI will be higher when CYP2E1 is induced and there is no ethanol present than the risk if ethanol is present.

“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].”


A “two bag” 12 h administration of acetylcysteine appears to be safer.

N-Acetylcysteine Treatment Nomogram for Paracetamol Overdose in Adults

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

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

Assessment Short Answer Question Examples

1. Give an example of a physical sign of drug poisoning and a medicine causing this.

2. Explain how activated charcoal may enhance the elimination of drugs.

3. What specific antidote may be used to treat cyanide poisoning?