POISONINGS WITH PHARMACEUTICALS AND MUSHROOMS

SYMPTOMATIC AND SUPPORTIVE CARE

- monitoring and pharmacological support of the circulation
- sufficient ventilation, oxygen
- correction of osmolarity, electrolytes and anion gap disturbances
- prevention of complications: aspiration bronchopneumonia, hypoxemia due to hypoventilation, seizures, renal failure due to nephrotoxic chemicals, due to hypoperfusion, position trauma

ANTIDOTE

- Binding or inactivating of a toxic chemical (chelating agents, sodium thiosulphate, immunological binding of digoxin)
- Interfering with the effect (oximes – activation of acetylcholin esterase by breaking the bond to organophosphate)
- Indication depends on the diagnosis and severity of intoxication
- Antidote is **always preferred** to extra corporal elimination.

Antidotes for cyanide intoxication

Nitramyl+4-DMAP+Na thiosulphate

Antidote for methemoglobinizing agents – Toluidinblau inj.

CHARCOAL

- **absorbs and inactivates toxins in the lumen** of GIT, but probably also **from the blood stream** through the wall of the vessel thanks to the negative gradient ("intestinal dialysis").
- **Charcoal not effective**: **highly ionised salts** (cyanides, iron, lithium, lead, mercury)
- and **small polar molecules** (alcohols, glycols), acids or alkalies ingestion
- **Contraindicated**: acid or alkali ingestion (endoscopy difficult), GIT obstruction.

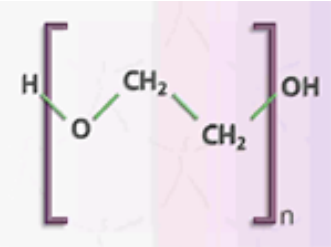
CHARCOAL for SECONDARY ELIMINATION

- **Mild intoxications**: low doses: 1 – 20 tbl.
- **Severe intoxications**: (toxic of lethal doses)
- – given in high doses of 1g/kg b.w. (1g=3 tbl.!)
- **Repeatedly:** ½ g/kg b.w. every 4-6 hours (enterosorption) – severe cases, drugs with long elimination half-live, slow-release or enterohepatic circulation.
- **Proven effect in**: carbamazepine, theofylline,phenobarbital,...
- In tricyclic antidepressants (TCA) where no antidotes exist.

FORCED DIURESIS

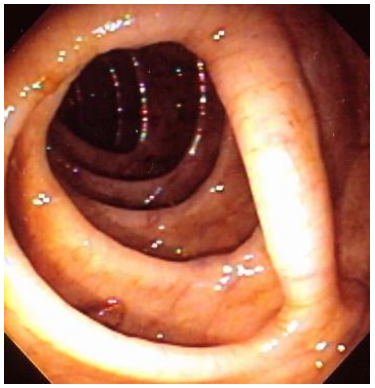
less used

- elimination of chemical excreted by the kidneys by tubular reabsorption,
- present in blood
- and with low binding to plasma proteins (**barbiturates, salicylates**)
- High risk in old patients, patients with cardiac and renal damage, in shock.



PEG - laxative

GIT dialysis



- PEG – polyethyleneglycol in balanced salt solution
- 4 litres/ 2 hours

- Polyethylene glycol electrolyte lavage solution is remarkably safe.
- Effective for slow-release tablets (euphylline, …), antidepressants (TCA)

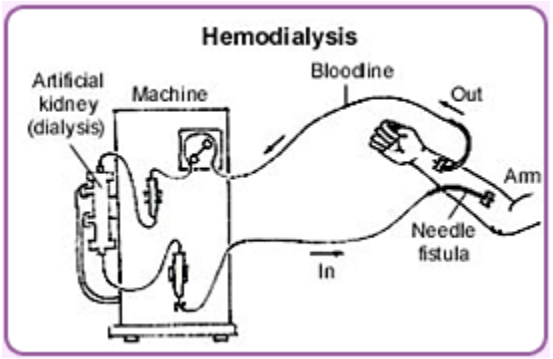
EXTRA CORPORAL METHODS

- in cases where antidotes cannot be given and where chemicals are

- **1) available in blood in high concentrations**

- **(not bound to the tissues proteins)**

HEMODIALYSIS

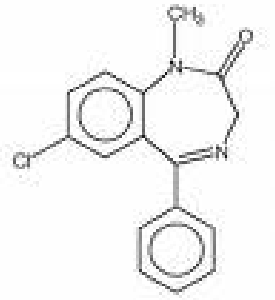


- Blood is pumped through the system where toxins **with small molecules** flow passively down the concentration gradient through a semi-permeable membrane
- into an electrolyte and buffer solution.
- Used for severe intoxication with: **lithium, methanol, ethylene glycol, ethanol, barbiturates, salicylates** (chemicals with small size, water solubility and low protein binding).

HEMOPERFUSION

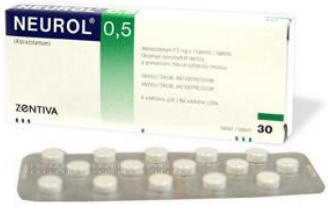
- Blood is pumped through a column with adsorbent material (**charcoal or synthetic resin**) – **even larger size of molecules.**
- Invasive, expensive method, systemic anticoagulation is required.
- Used for severe intoxication with: **barbiturates, theophyllin, digoxin** (drugs that are sufficiently bound by charcoal or synthetic resins)**.**

BENZODIAZEPINS

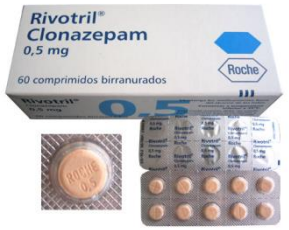


- Diazepam, oxazepam, chlordiazepoxide, medazepam – sedatives, hypnotics
- Frequent suicidal attempts
- **Pathogenesis:** generalised depression of spinal reflexes and the reticular activating system by enhancing of the inhibitory neurotransmitter GABA.

- **Symptoms:** CNS depression within 30-120 minutes - lethargy, ataxia, hypotension, coma,
- rarely respiratory arrest



BENZODIAZEPINS



Long-lasting effect elimination half-life (longer than 1 day).

- **Diazepam, Seduxen, Apaurin (diazepam)**
- **Defobin (chlodiazepoxid)**

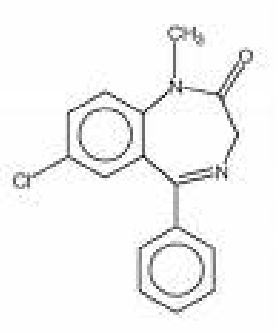
Medium:

- **Neurol, Xanax (alprazolam)**
- **Lexaurin (bromazepam)**
- **Rivotril (clonazepam)**

Short-term elimination half-life less then 12 hours

- **Oxazepam (oxazepam)**
- **Dormicum (midazolam)**

BENZODIAZEPINS



- **Toxicity – relatively low:**
- 20 fold therapeutic dose cause mild symptoms,
- 60 fold can be lethal
- Therapy: charcoal, emergency and supportive measures,
- **Antidote: flumazenil (Anexate) inj.**

- used only to reverse coma.
- *Caution: in mixed overdoses the antidote may provoke seizures !! (tricyclics,..theophyllin,..)*

PARACETAMOL=ACETAMINOPHEN

Frequent ingestions: suicides, children

- **Toxicity:** 100 mg/kg may be hepatotoxic in vulnerable persons (low nutrition, alcoholics - increasing with P 450 induction, antitbc medication,..), otherwise 200 mg/kg
- LD 10-20 g (20-40 tbl!) depending on the body weight
- **Symptoms:**
- Day 1: in few hours nausea, vomiting,
- Day 2: improvement (!)
- Day 3: progression of hepatic and renal damage, failure, encephalopathy, death.

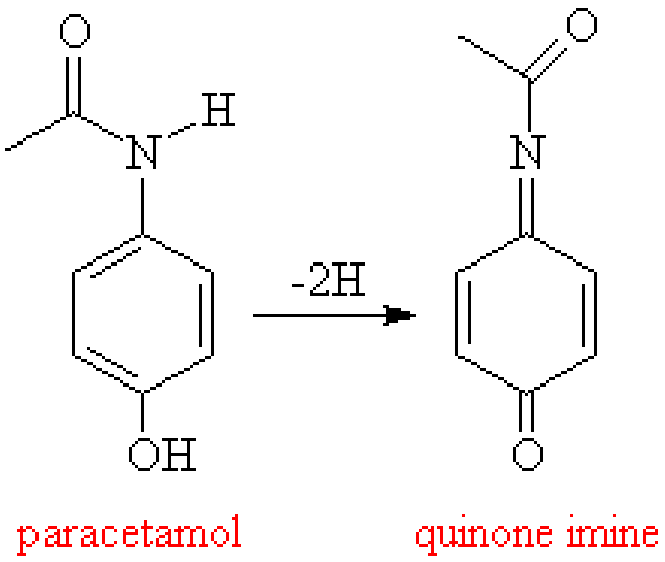
PARACETAMOL - 1

Pathogenesis: one of its oxidative metabolites

N-acetyl-*p*-benzochinonimin - NAPQI is hepatotoxic.

Normally formed in 4% by cytochrome P 450, and is conjugated with GSH.

In overdose detoxification of NAPQI is unsatisfactory- necrosis in liver and kidneys

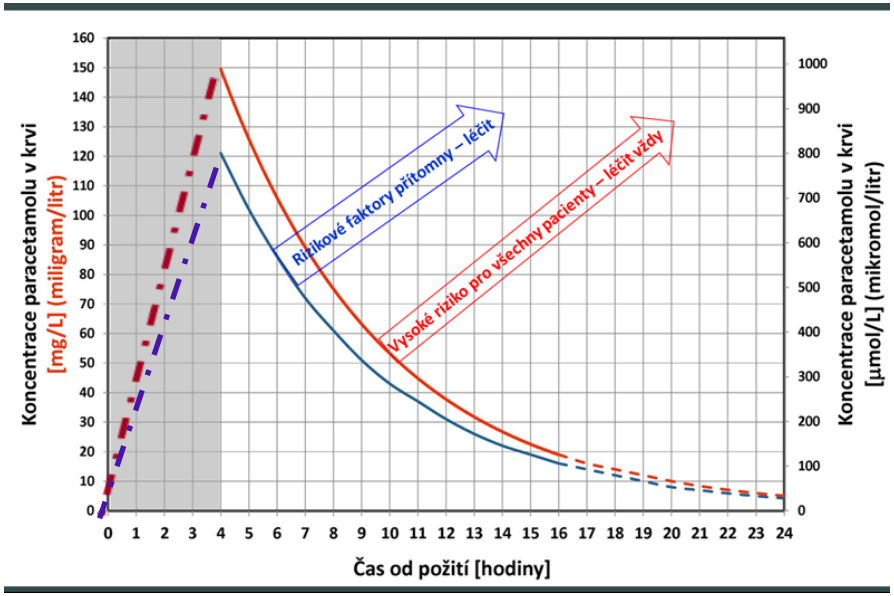


PARACETAMOL – 2

- **Treatment:**
- gastric lavage until 1 hour after ingestion
- charcoal 1g / kg body weight **once** (paracetamol has a short half-life of 3 hours, is rapidly eliminated)
- Prokinetics - metoclopramid (Cerucal, Degan) in case of intense vomiting
- **Antidote N-acetylcystein (ACC inject.)** i.v. or per os, in case of hepatotoxic plasma levels of paracetamol.

Nomograme for hepatotoxic damage due to paracetamol in blood – dose-response

NAC

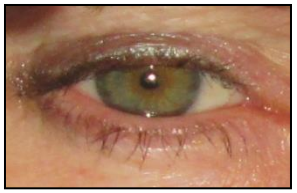


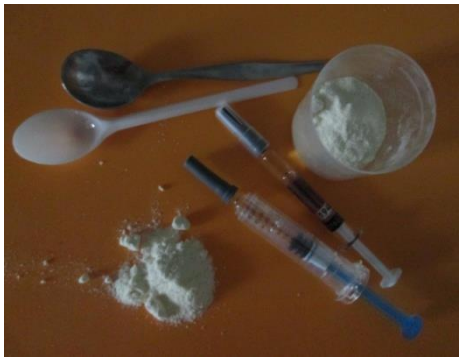
Measure blood paracetamol at 4 hours after ingestion

If over 150 mg/l, give NAC in all patients;

if over 120 mg/l, give NAC to vulnerable patients.

MORPHIN, OPIATES AND OPIOIDS



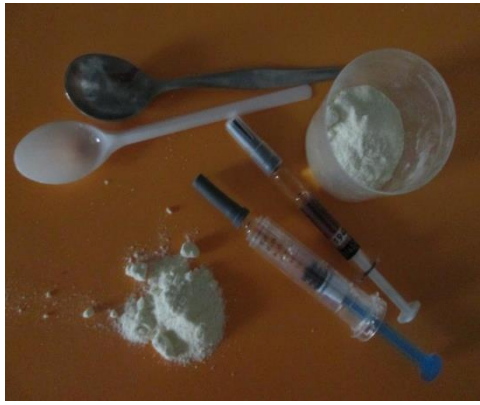


- **Morphin, codein, heroin, tramadol,..**

- **Pathogenesis:** stimulation of specific opiate receptors in CNS
- **Toxicity**: large variability, tolerance in chronic abusers
- LD extremely individually different (15 mg – 3000 mg).
- Dose frequently unknown, purity????

- **Symptoms:** euphoria, sedation, lethargy, miosis - pinpoint pupils, coma, respiratory depression apnoea, and sudden death

MORPHIN, OPIATES AND OPIOIDS

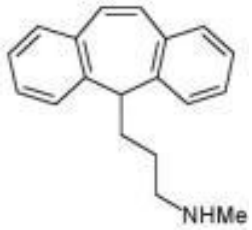


- **Treatment:**
- Gastric lavage and repeated dose of charcoal 50 g/ 4hours in case of oral route
- **Antidote naloxone (Intrenone)** i.v. for coma or respiratory depression.
- Effect for 2-3 hours only, shorter half-life than the opiate, given repeatedly, if necessary.
- Supportive and symptomatic care

CYCLIC ANTIDEPRESSANTS

- Frequent suicidal intoxications
- **Mechanism**: increase the level of free monoamines by inhibition of neuronal reuptake of catecholamines.

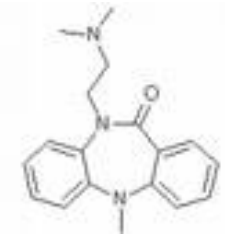
I. Generation – Tricyclic Antidepressives



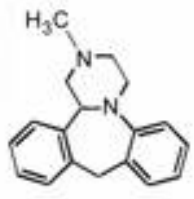
- **imipramin**, **amitriptylin- most cardiotoxic**
- already 10 fold therapeutic dose is dangerous.

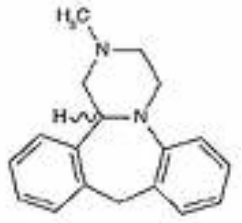
II. Generation – medium toxicity

- **Tricyclic dibenzepin** - Noveril



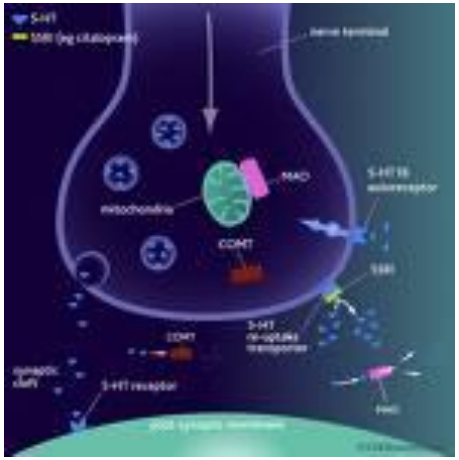
- **Tetracyclic: maprotilin -** Ludiomil
  mianserin - Lerivon)



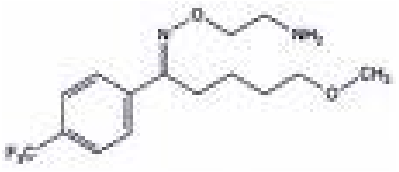


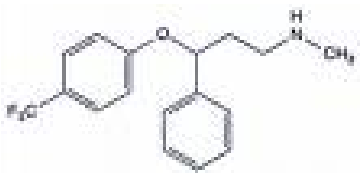
CYCLIC ANTIDEPRESSANTS

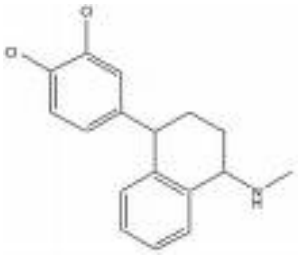
III. Generation SSRI

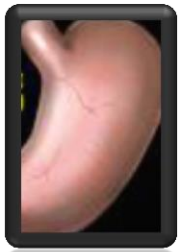


- Selective Serotonin Reuptake Inhibitors - lowest toxicity.
- **fluvoxamin** - Fevarin
- **fluoxetin -** Seropram**,** Prozac
- **sertralin -** Zoloft and others)









CYCLIC ANTIDEPRESSANTS

1) ANTICHOLINERGIC – mydriasis, dry skin, excitation, delirium, diminished bowel sounds, urinary retention, diminished sweating

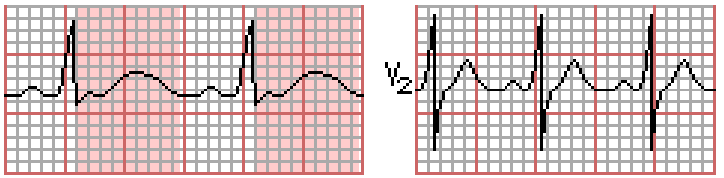
   Slow uptake due to anticholinergic action

Gastric lavage – useful even after 4 hours!

2) CARDIOVASCULAR TOXICITY – first sign: prolongation of the QRS complex above 100 ms, tachycardia, arrhythmias ventricular fibrillation

3) SEIZURES, hyperthermia,

4) CNS toxicity, COMA, death

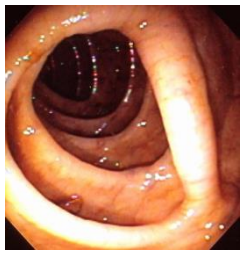


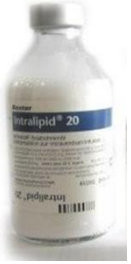
CYCLIC ANTIDEPRESSANTS

- Elimination half-life: 20 – 30 hours
- Highly plasma and tissue proteins bound – distributed into a large volume
- HD and HP not effective

TREATMENT

- **no antidote**
- Gastric lavage –until 4 hours effective!
- Activated charcoal 1g/kg b.w.(repeatedly every 2-4 hours)
- Laxative with PEG (Fortrans)
- Symptomatic treatment
- Monitoring EKG and support of vital functions
- (diazepam for treatment of seizures)





LIPID RESCUE THERAPY

- LIPID **EMULSION**

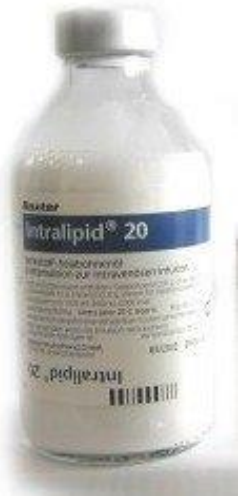
for the therapy of severe dysrhythmias (ventricular tachycardia, sinus fibrillation, asystolia)

in LIPIDS SOLUBLE DRUGS

- Free fraction of the drugs binds to the lipid and the pharmacological effects lowers

- Used already for local anesthetics: *lidocaine, trimecaine*

LIPID THERAPY

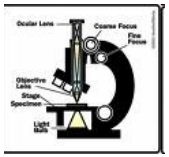


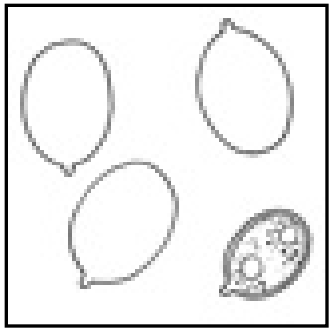
- **DOSING:**
  1 ml/kg 20% Intralipid i.v. bolus …… 70 ml
  than infusion 3 ml/kg/h …… 200 ml/hod
- **total dose/adult…… 500 ml**
- **Lipophilic drugs:**
- some betablockers (*bopindolol, carvedilol*, *nebivolol*)
- some Ca channel blockers (*verapamil, amlodipin, diltiazem*)
- some antidepressants: *amitriptyline, dosulepin (TCA), sertraline*

http://www.lipidrescue.org

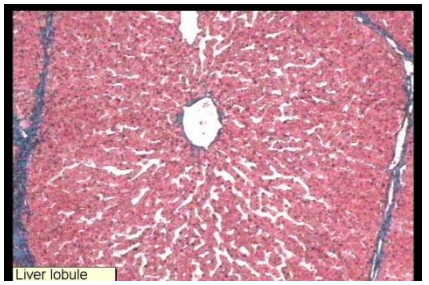
AMATOXIN-TYPE Amanita phalloides

- **Pathogenesis: amatoxins** inhibit protein synthesis by interfering with RNA polymerase.
- Typically late onset of symptoms: 8-12 hours
- Intense repeated diarrhoea and vomiting
- Hepatic failure, kidney failure
- Diagnosis: microscopic mycological
- analysis - typical spores





Amanita phalloides,



- **Liver and kidney failure**
- **Lethal dose**
- 0.1 mg/kg of amatoxin = one cap of Amanita!

Treatment

- Gastric lavage not necessary due to repeated vomiting),
- Repeated high doses of charcoal 50g/4hod for 3-5 days,
- oral fluids, i.v. crystaloid solutions, glucose,
- K_1 vitamine
- **Antidote** for 3-5 days:
- **silibinine (Legalon SIL) inj**. – restores activity of RNA-polymerase, stops entering the toxins to the liver cells and helps their elimination from the liver, **or N-acetylcysteine**
- **No indication of HP or HD** (amatoxins early disappear from blood)
- Liver transplantation in severe cases

AMANITA MUSCARIA, A. PANTHERINA

- **Toxins:** Ibotenic acid, muscimol
- **Onset of symptoms**: rapid - 0.5-2 hours
- Neurotoxicity
- **Symptoms:** muscular jerking, anticholinergic syndrome, **hallucinations**, impaired consciousness , COMA
- **Therapy:** symptomatic, intensive care, sedatives

PSILOCYBE

(*Lysohlávky)*

Toxin: psilocybin
Inset of symptoms:
rapid **-** 0.5-1 hour
Symptoms:
hallucinations
Therapy:
Charcoal,
diazepam,
symptomatic

Cortinarius orellanus

(*Pavučinec plyšový*)

- Nephrotoxic mushroom –orellanin
- Late onset of symptoms:
- Kidney failure 3 weeks
- after ingestion
- Symptomatic treatment
- (irreversible - hemodialysis
- for kidney
- failure, transplant)