

Antodots and treatment of intoxications

PharmDr. Milan Juhás

...before we begin

- ▶ Toxicology information centre in Prague
 - ▶ 224 919 283, 224 914 570

- ▶ Snake poisoning consult centre in General University Hospital in Prague
 - ▶ 224 962 244





Intoxication



Intoxication
treatment

Causal

Symptomatic

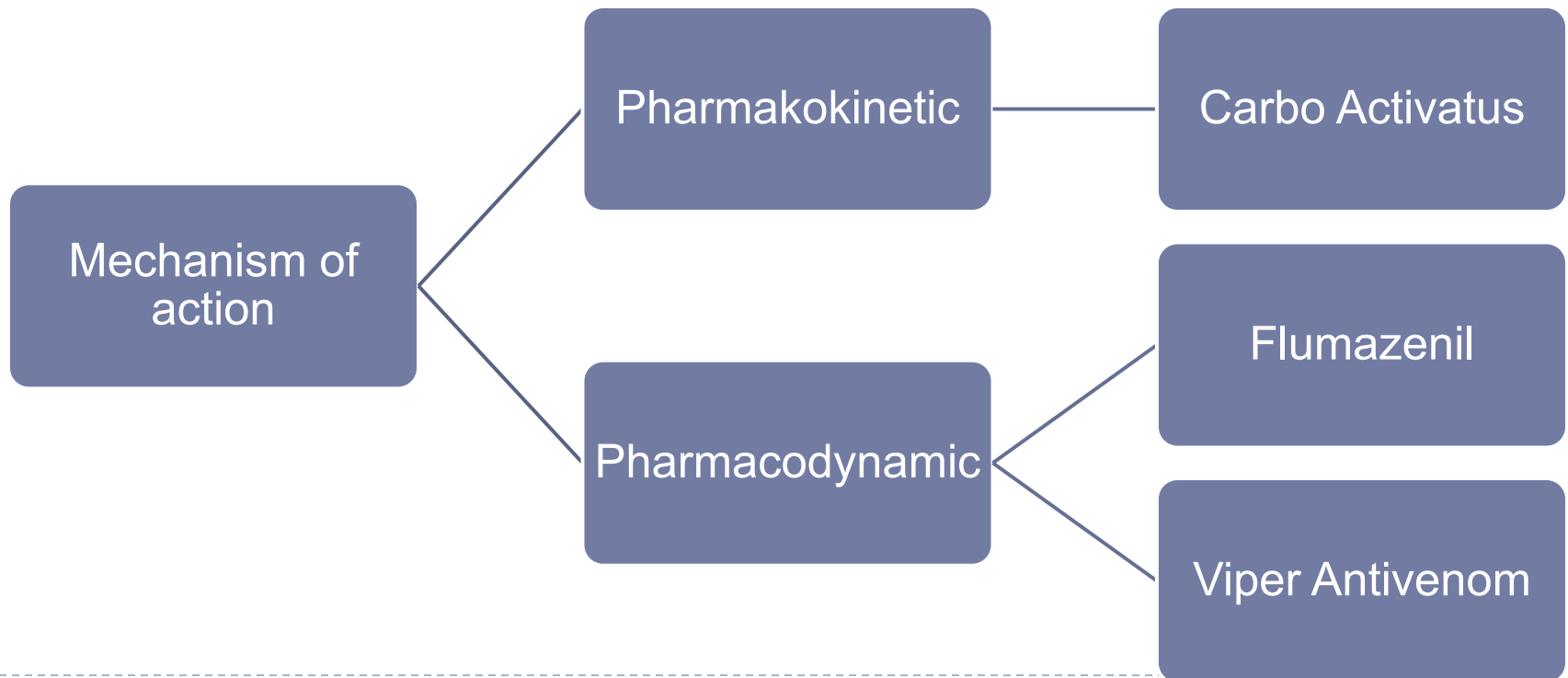
Administration
of antidote

Stabilisation
and support of
vital functions



Necessary definitions

- ▶ What exactly are „Antidots“ ?
 - ▶ Drug or substance with **opposite effect to poison** or **venom**, which administration is expected with improvement of vital functions impaired by intoxication

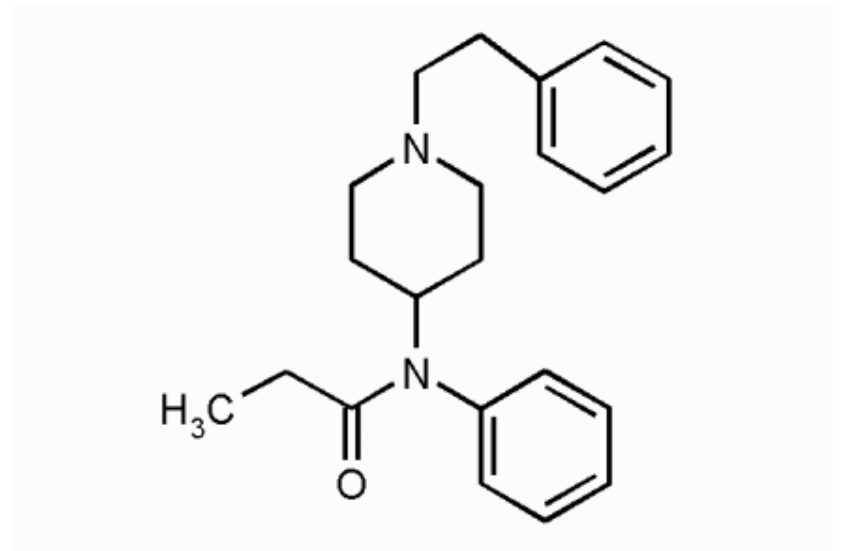
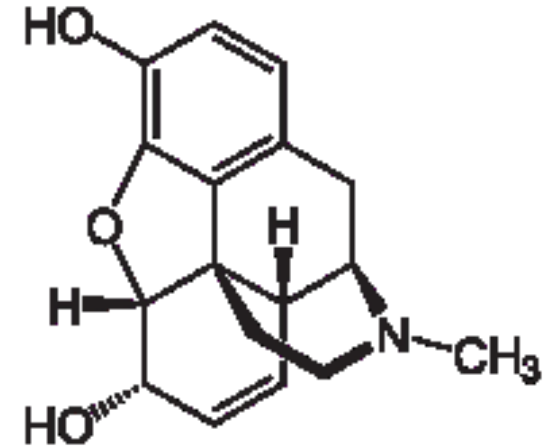
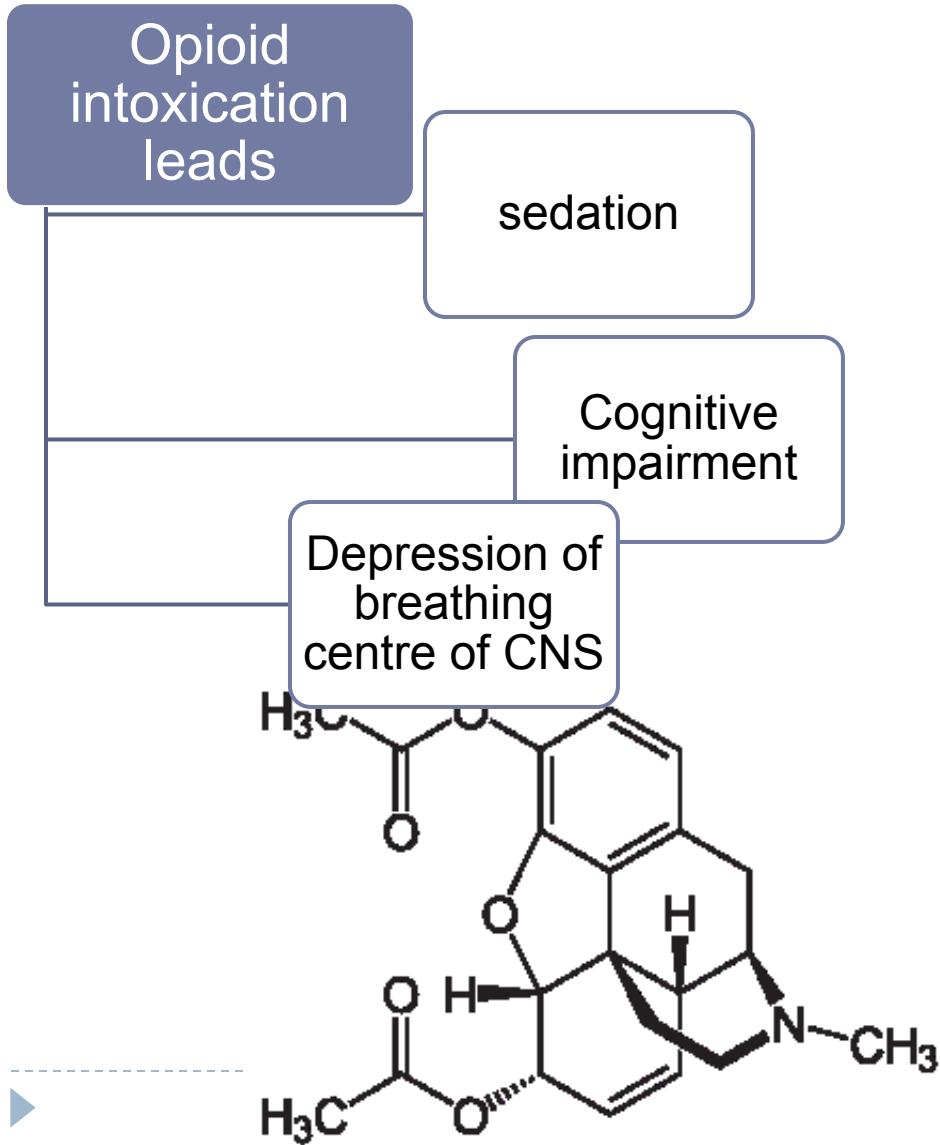


Antidots available in Czech republic

Amanita Phalloides toxin	Silymarin, hepatoprotectives
Morphin and morphinomimetics (Narcotics)	Naloxone, Naltrexone
Atropin, anticholinergics	Physostigmine
Benzodiazepines	Flumazenil
Digitalis	Digitalis Antitoxin
Glycoles (polyoles)	Etanol
Warfarin and Coumarines	Vitamin K ₁ ,
Cyanides	Amylum nitrosum, Hydroxycobalamine
Methemoglobinizing agents	Toluidine blue
Methanol	Etanol, Folic Acid
Lead	Succimer
Organophosphates	Atropin, obidoxime (AChE reactivators)
Paracetamol (Acetaminophen)	N-Acetylcysteine
Mercury	Unithiol
Viper venom	Viper Venom Antitoxin ®
Iron	Desferioxamin

Universal Antidot - Carbo activatus

Opiates and narcotics



Opiates and narcotics

▶ Symptoms

- ▶ Somnolence, miosis, nausea, vomitus
- ▶ Euphoria is strongest after Heroin
- ▶ Intestinal hypomotility and *constipation (chronic use)*

▶ Selective antidotes

- ▶ Naloxone
- ▶ Naltrexone
 - ▶ Necessary to administer until is secured hepatal elimination of narcotic

▶ Route of administration is crucial for proper pain management and minimazing risk of intoxication

- ▶ (from the patient point of view) – i.v., per os, nasal



Management of withdrawal syndrome

- ▶ Heroin addiction and overdose
 - ▶ Opioid antagonist (NLX, NTX)
 - ▶ Spasms and anxiety
 - ▶ Diazepam
 - ▶ Haloperidol
 - ▶ Tiaprid



Atropin, Scopolamine, L-Hyocyamine (Tropan alkaloids)

- ▶ naturally occurrence in *Datura stramonium*, *Atropa belladonna*
- ▶ Direct antagonists of Ach in parasymphatikus
 - ▶ Skin erubescence, mucose dryness (severe xerostomia), tachycardia, mydriasis, misorientation, urine retention, coma



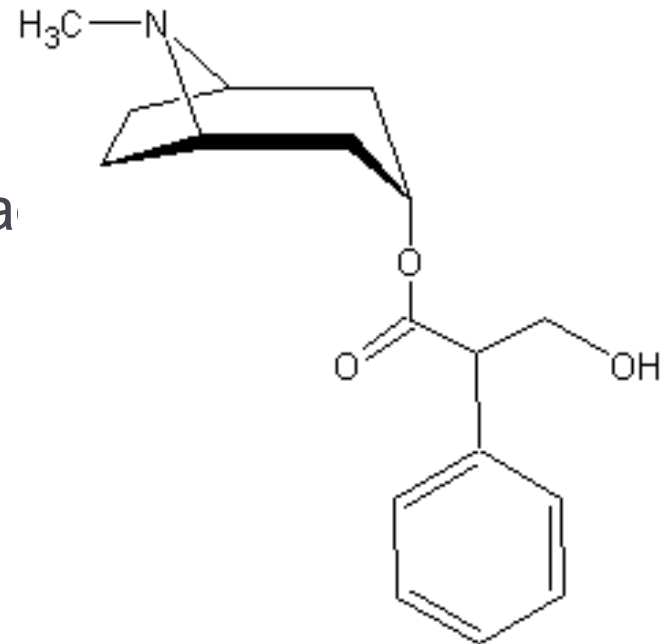
Atropin, Scopolamine, L-Hyocyamine (Tropan alkaloids)

- ▶ **Causal therapy**

- ▶ Administration direct antagonist – physostigmin

- ▶ **Symptomatic therapy**

- ▶ Beta-blockers (atenolol)
- ▶ Carbo activatus and stomach lava



Anticholinergic agents (1st generation antidepressants)

- ▶ **Tricyclic antidepressant agents**
 - ▶ Inhibition of serotonin and noradrenaline uptake
 - ▶ Dosulepin, Amitriptylin, Imipramin

 - ▶ Intoxication induces anticholinergic syndrome
 - ▶ Xerostomia, mydriasis, tachycardia,
 - ▶ sedation, expansion of QRS complex

- ▶ **Antidote – None**
 - ▶ High dose of carbo activatus
 - ▶ Symptomatic therapy till improvement



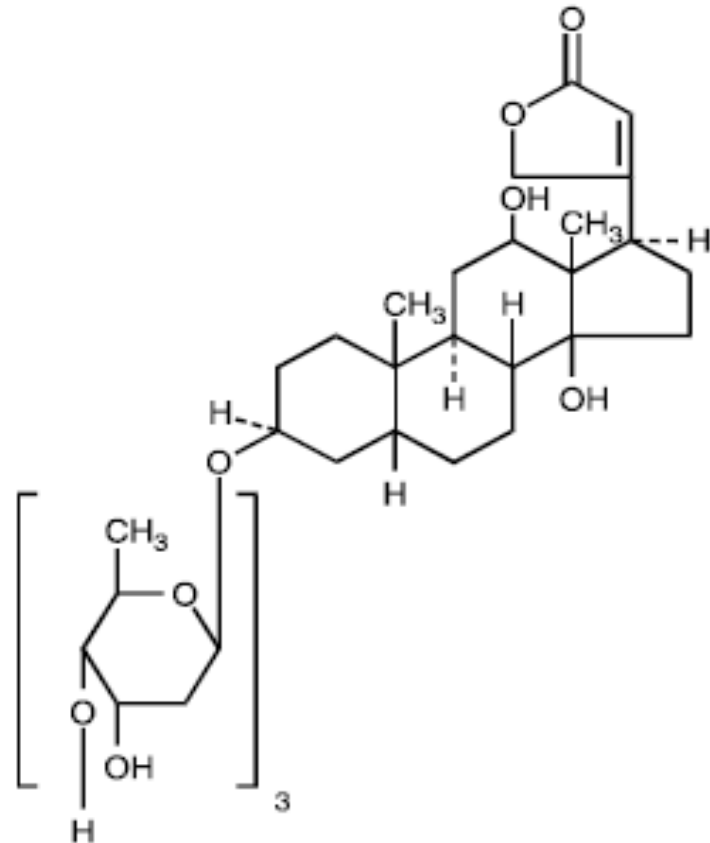
Sedatives and hypnotics

- ▶ Anticonvulsant and myorelaxant activity
- ▶ Benzodiazepines
 - ▶ Alprazolam
 - ▶ Bromazepam
 - ▶ Diazepam
- ▶ Non-BZD hypno-sedatives
 - ▶ Zolpidem
 - ▶ Zopiclon
- ▶ Symptoms
 - ▶ Somnolence, ataxia and hypotension
 - ▶ Escalation of pharmacodynamic effect on GABA receptor –
coma
- ▶ Antidot for both BZD and non-BZD hypno-sedatives
 - ▶ **Flumazenil** – antagonist on GABA receptor



Digoxin and cardiac glycosides

- ▶ *D. Purpurea, D. Lanata,*
- ▶ Cardiotonicum,
antiarrhythmic agent
- ▶ Atrial fibrillation
- ▶ Heart failure
- ▶ Therapeutic drug
monitoring



Management of digitalis toxicity

Digitalis Pharmacokinetic parameters

High level of plasma protein binding

Large distribution volume



Digitalis pharmacodynamic parameters

Na/K ATPase block

Arrhythmogenic potential



Strategy of treatment

Dialysis is ineffective

Antidote – digitalis antitoxin



Symptoms of digitalis toxicity

- ▶ Hypokalemia – increased potassium kidney elimination
- ▶ Nausea, vomiting
- ▶ Color perception disorder – yellow sight
- ▶ dizziness, arrhythmia

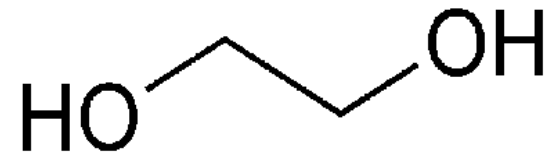
- ▶ Strategy
 - ▶ Discontinue digoxin administration
 - ▶ In severe cases apply antitoxin



Management of glycol intoxication

▶ Glycols

- ▶ Carbohydrates with more than one OH functional group
- ▶ Hepatal metabolism converts glycolsto oxalic acid and to calcium oxalate
- ▶ Risk of metabolic (chemical damage) acidosis and renal damage by precipitated calcium oxalate



Management of glycol intoxication

- ▶ Symptoms

- ▶ Renal

- ▶ Hematuria , albuminuria, acute tubular necrosis, anuria

- ▶ Non-renal

- ▶ Metabolic acidosis, hypocalcemia, spasms, dysrhythmias

- ▶ Ethyleneglycol metabolised by alcoholdehydrogenase

- ▶ Antidotum – ethanol

- ▶ Ethyleneglycol eliminated by kindeys in unchanged form

- ▶ During threatment with ethanol, correction of metabolic acidosis and calcium supplementation is required



Lead poisoning

▶ Toxicity of Lead

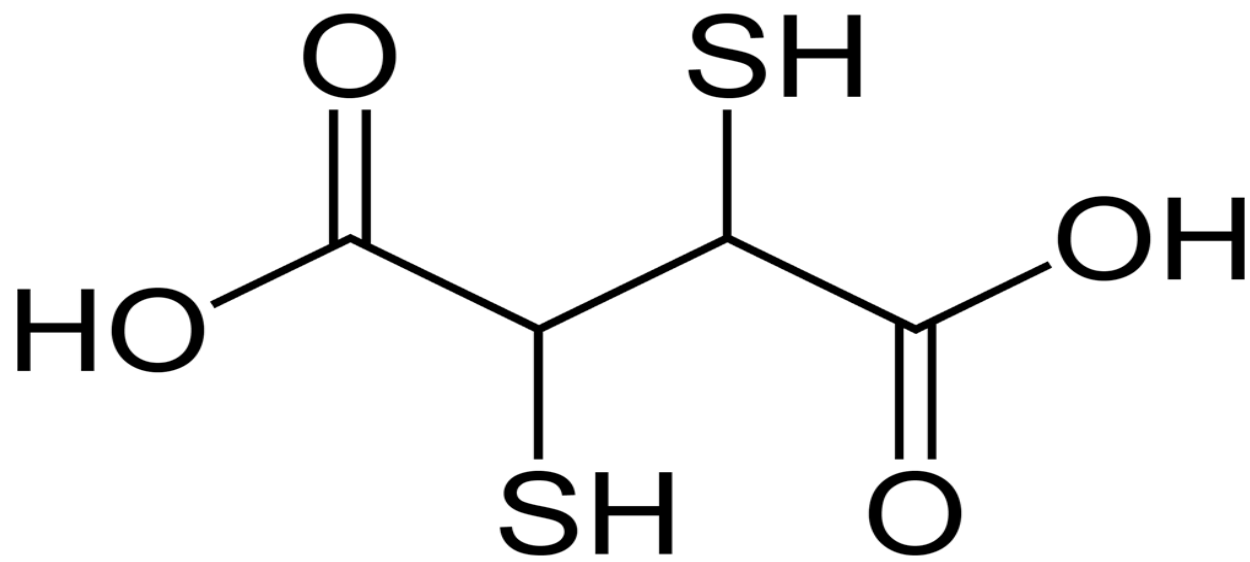
- ▶ Ligation to haemoglobin
- ▶ **Inhibition of haem synthesis** (block of 5-ALA-synthase)
 - ▶ Accumulation of koproporphyrines

▶ Results to

- ▶ Sideroblast anaemia, neuropathy and constipation

▶ Threatment

- ▶ Chelation by DMSA (dimercaptosuccinic acid) and elimination through kidneys, EDTA
 - ▶ Organic forms of lead do not respond to chelation (penicilamine ?)
-



Mercury poisoning

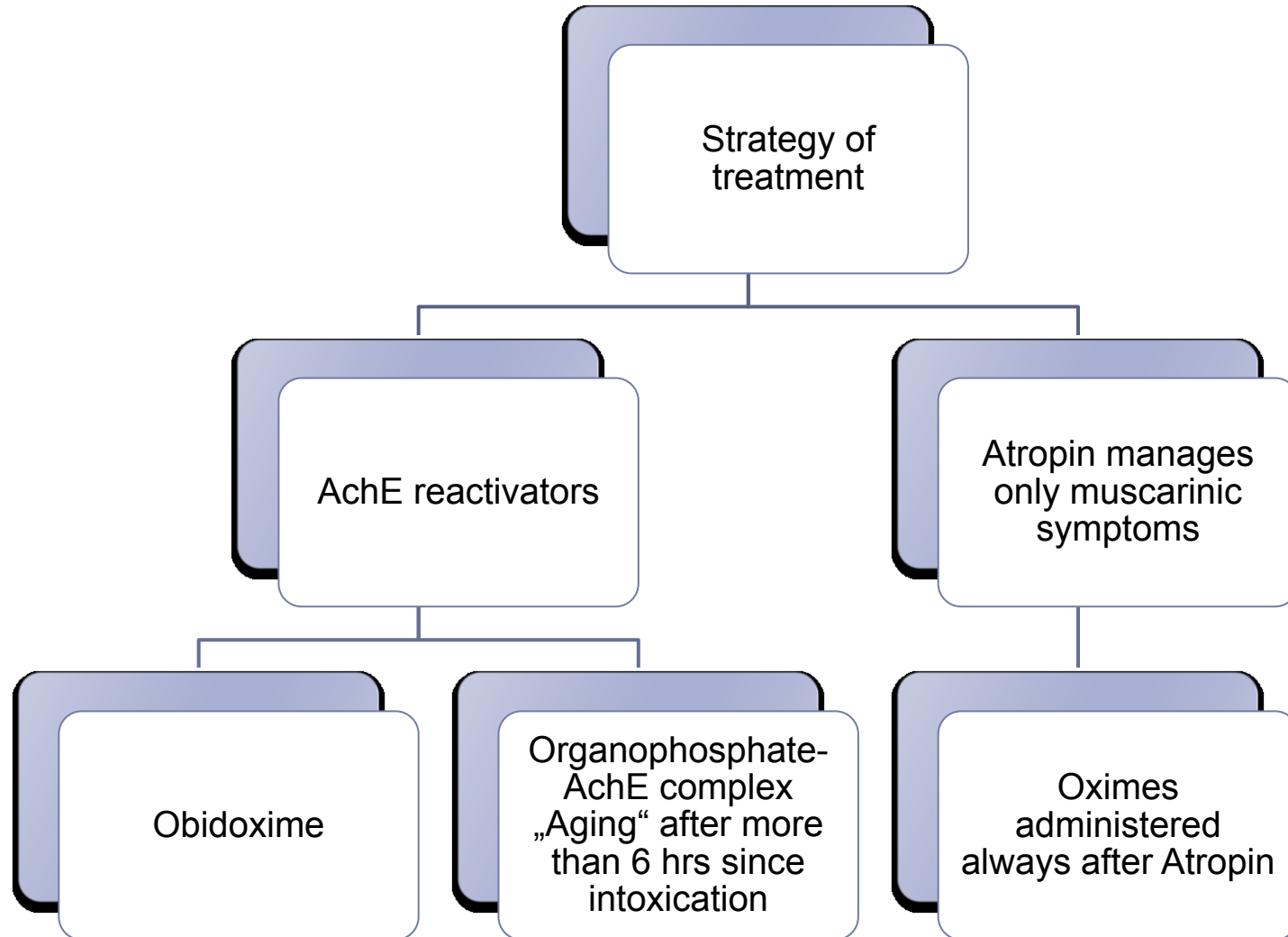
- ▶ form ion Hg^{2+} in mercury chloride and mercury nitrate
 - ▶ Route on intoxication through lungs
 - ▶ Central neural toxicity (tremor, sleep inversion, eretism)
- ▶ Treatment with chelation
 - ▶ Unithiol – dimercaptopropan sulphate



Organophosphates poisoning

- ▶ Esters of phosphoric acid with carbohydric alcohols (methanol), which cause irreversible inhibition of AchE
- ▶ Irreversible inhibition of AchE, which results to its toxicity
 - ▶ Cumulation of acetylcholine
 - ▶ Symptoms of parasympatomimetic stimulation
 - ▶ **Muscarine**
 - salivation, bradycardia, miosis, nausea, vomitus, lacrimation, diarrhoea
 - ▶ **Nicotinic**
 - Desorientation, spasms, coma

Organophosphates poisoning



Carbamate insecticides

▶ Carbamates

- ▶ Competitive inhibitors of AchE
- ▶ Poisoning is **similar** to Organophosphates

- ▶ Atropin administered in individual dose according to improvement.
- ▶ Management of adverse phenomenon
 - ▶ Symptomatic therapy

- ▶ Administration of Oximes is not necessary



Methemoglobinemia agents

- ▶ Aromatic and alifatic organic amines (Aniline, etc.)
- ▶ Nitroarenes (nitrobenzene, etc.)
 - ▶ Industrial substances to prepare explosives, when ingested, causing oxidation of iron in Haemoglobin
 - ▶ Fe^{2+} to Fe^{3+}
- ▶ **15 – 30 %** damaged haemoglobine
 - ▶ Cyanosis, tachycardia, fatigue
- ▶ **30 – 50 %**
 - ▶ Weakness, dyspnoe, headache
- ▶ **50 – 70 %**
 - ▶ Cognition impairment, death



Antidotes and treatment

- ▶ Chemical reduction of Fe^{3+} to Fe^{2+}
 - ▶ symptoms
 - ▶ Dyspnoea, fuzziness, chest pain
- ▶ Thiazine colours
 - ▶ Toluidin blue 3 % solution i.v.
 - ▶ Methylene blue 1% solution i.v.
 - ▶ Donors of electrons necessary for NADPH- dependent mechanism of methemoglobin-reductase enzyme
 - ▶ Risk for patients with congenital GLUCOSE-5-PHOSPHATE DEHYDROGENASE deficiency
- ▶ Indication of Thiazines administration is concentration of methemoglobin above 25 %



Inhalation trauma

- ▶ First Aid !
- ▶ Administration of oxygen

- ▶ In case of bronchospasm
 - ▶ Beta₂-mimetics (formoterol, **salbutamol**)
 - ▶ Inhalation spasmolytic agents (ipratropium bromide)

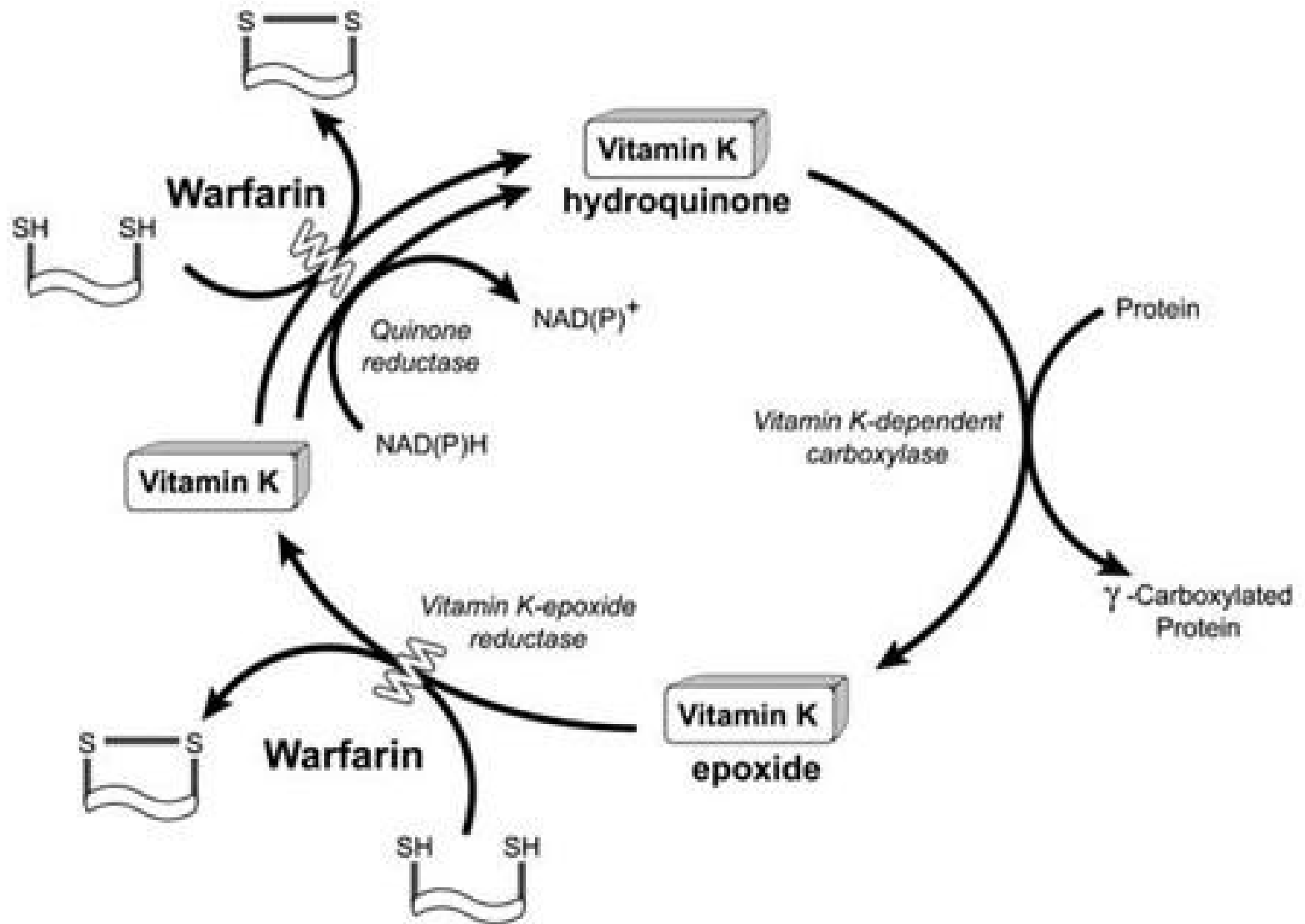
- ▶ Inhalation of corticosteroids is **obsolet** and has no effect



Warfarin

- ▶ Anticoagulant widely used in many coagulopathies
 - ▶ Necessary periodic monitoring of INR
 - ▶ High risk of drug-drug interactions
 - ▶ 3 day latency
 - ▶ Competitive inhibitor of vitamin K-mediated synthesis of coagulation factors (II, VII, IX, X)
- ▶ Antidote – vitamin K





Iron intoxication

▶ GI tract disorder

- ▶ Haemorrhagic gastritis, black vomitus and severe stomach pain
- ▶ **Severe constipation** and circulation colaps

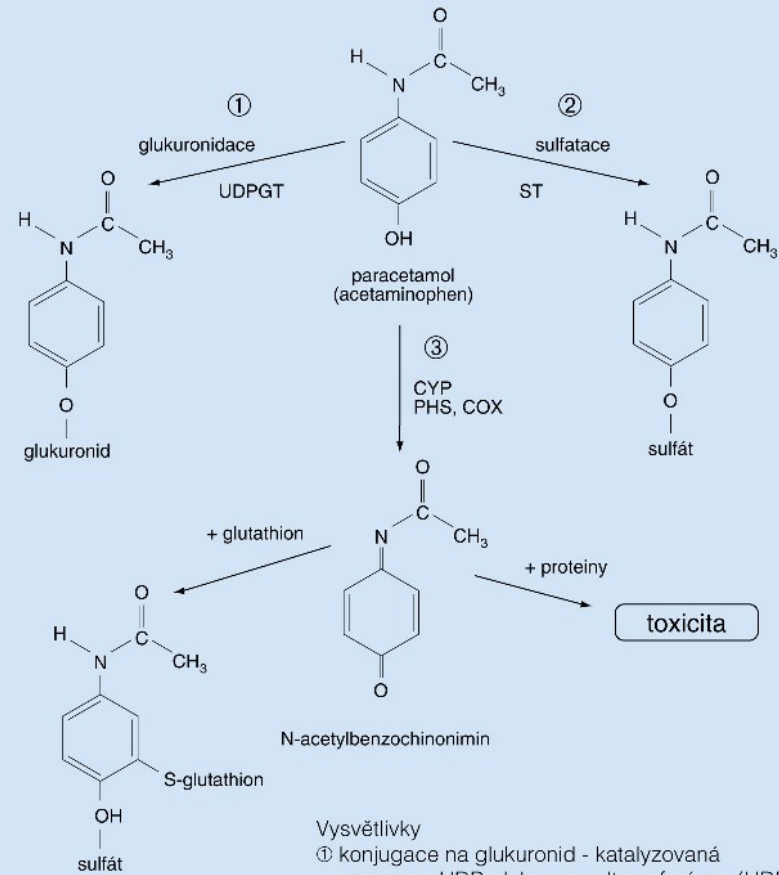
▶ Antidotum

- ▶ Chelation using **deferoxamin**
 - ▶ i.v. , i.m.
 - ▶ per os with gastric scope
- ▶ Symptomatic therapy to secure vital functions and prevent shock



Paracetamol (Acetaminophen)

SCHÉMA ZÁKLADNÍCH METABOLICKÝCH PŘEMĚN PARACETAMOLU



detoxikace

Vysvětlivky

- ① konjugace na glukuronid - katalyzovaná enzymem UDP-glukuronosyltransferázou (UDPGT)
- ② konjugace se sulfátem - katalyzovaná fenolsulfotransferázou (ST)
- ③ oxidace na benzochinonimin - za účasti cytochromu P-450 (CYP) a cyklooxygenázy (COX - též prostaglandin H syntáza, PHS)

Toxicity of paracetamol

- ▶ Toxic dose 140 – 150 mg/kg
 - ▶ Nausea, vomitus, hepatotoxicity,
 - ▶ After 24 hrs of no treatment lead to hepatorenal syndrome with hepatal and renal failure
- ▶ High dose of carbo activatus, hepatoprotectives
 - ▶ (N-acetylcysteine),
- ▶ In case of vomitus (ondansetrone)
- ▶ Therapy *in cursu* till normalisation of hepatic markers



Methanol intoxication

- ▶ Dangerous substitution for ethanol
- ▶ Metabolized with same alcoholdehydrogenase to **formic acid** (toxic metabolite)
 - ▶ Individual dose due to activity of Alcoholdehydrogenase and capacity of folic acid
 - ▶ Cummulation of formic acid lead to damage of retina
- ▶ **Early symptoms**
 - ▶ Drunkness, gastritis
- ▶ **Late symptoms**
 - ▶ blindness (after 30 hrs), spasms, coma, death
- ▶ Antidote – **ethanol**
 - ▶ Formic acid creates with ethanol ester, which is harmlessly eliminated by kidneys



Carbo activatus as universal antidote

- ▶ Prepared by pyrolysis of plants
- ▶ Characteristic with its high absorption surface (3700 m²/g)

- ▶ Mechanism of effect
 - ▶ Absorption
 - ▶ Secondary elimination of toxins from bloodstream

- ▶ Lack of effect with high-polar molecules
 - ▶ Lithium, glycoles





▶ Indications

- ▶ Poisons with enterohepatal circulation
- ▶ Severe intoxications without dialysis's perspective
- ▶ Slow-release drug forms (repeatedly)

▶ Contraindications

- ▶ Intoxication with irritative poisons (acid, lye)
 - ▶ Cognitive impairment and airways blockage
 - ▶ GI obstruction
- ▶ Carbo activatus is without any severe adverse effect, in rare cases can cause constipation.

milan.juhas@fnusa.cz

