OCCUPATIONAL TOXICOLOGY

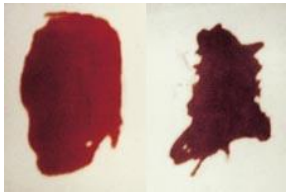
Methemoglobinizing agents, Cyanides, Carbon monoxide

METHEMOGLOBINIZING AGENTS

- MetHb (FeIII)- oxidized form of hemoglobin (FeII)
- Several oxidative chemicals and drugs are capable of inducing MetHb

(frequently contain N in the molecule)

normal X 15% metHb

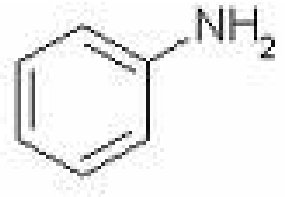


- 10-30 % tachycardia, fatigue
- 30-50 % brown blood, blue cyanosis, dyspnea, headache
- 50-70 % confusion, seizures, coma, death

„Blue Avatar family“

Deficit of G6P-Dehydrogenase

EXPOSURE

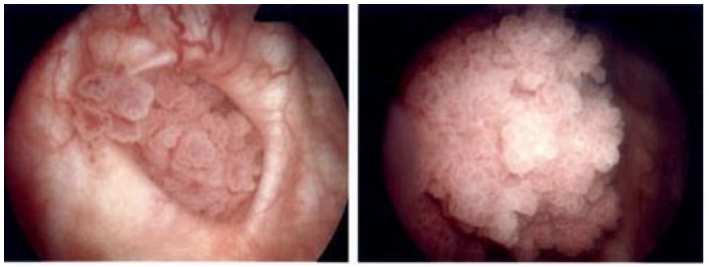


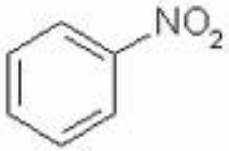
1. ANILINE (benzene-NH_2,
- oxidative metabolite phenylhydroxylamine)
- + ANILINE DERIVATIVES (aromatic amines, $=NH_2$, benzidine, 4-aminobiphenyl, 1-naphtylamine)

(reactive oxidative metabolites hydroxylamines– catalyzers of Hb oxidation)

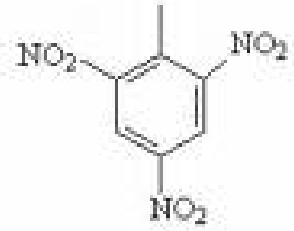
carcinogens – urinal bladder cancer

- industry of paints,
- pharmaceutical industry,
- rubber, plastics industry





EXPOSURE



2,4,6-trinitrotoluene

2. NITROBENZENE AND DERIVATIVES (trinitrotoluene, trinitrophenol=picric acid)

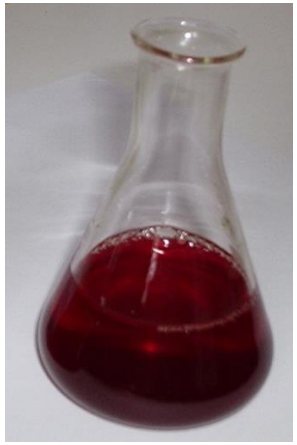
- Production of explosives
- rubber, pharmaceuticals

3. INORGANIC NITROGEN COMPOUNDS nitrogen oxides, vapours of nitric acid, esp. -NO_2 group

4. PHARMACEUTICALS:

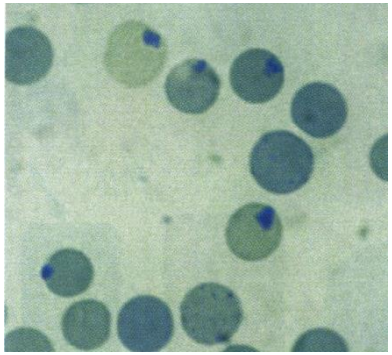
- Na nitrite, amylnitrite, 4-DMAP- cyanide antidotes.
- Antimicrobials: chloroquine (antimalarics), sulfonamides, dapsone (Mycobact. leprae), phenacetine.

FINDINGS

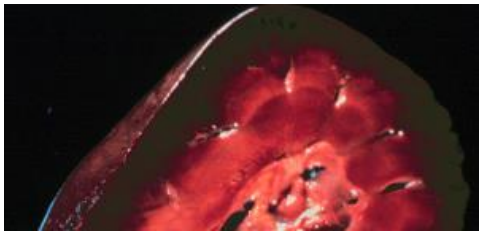


1. MetHb –Fe oxidation (brown-black blood)

2. Reactive oxygen species formed in ery, damaging it´s structure
   oxidation and denaturation of the protein part of Hb
   Heinz bodies in erythrocytes-
- hemolysis, hemoglobinuria



3. Acute tubular necrosis (pigment nephropathy)



METHEMOGLOBINIZING AGENTS

- **Treatment : reduction agents**
- Toluidine blue inj
- Methylene blue inj.

thiazine dyes, accept electron from NADPH and reduce into a leuko form – then the electron is given to Fe III which reduces to Fe II

- Caution: In case of too much antidote it accepts electron from Fe II and causes its oxidation !!

- Ascorbic acid may be used – but has slow and mild effect only

Dark blood and green urine

CYANIDES

Exposure:

HCN – gas above 23˚C fires, lighter than air, formed during burning of plastics with nitrogen in the molecule (acrylates, urethanes), wool, wood,

HCN deratization (rats control) in the silos (grain)

Inorganic cyanide salts NaCN, KCN – common laboratory reagents, photography

- Lethal dose: ¼ g (top of a knife)

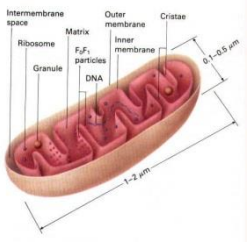
Amygdalin (bitter almonds,

- only traces of amygdalin
- in apricot and peach seeds)

Electroplating with cyanides

Cyanide salts of Au, Ag, Cu – water soluble - electroplating, gold extraction

Cyanides - pathogenesis



- reversible binding on the cytochrome oxidase (Fe^{III}) – it´s inhibition
- terminal of the mitochondrial respiratory chain (rapid effect in the brain!)
- CNS is the target for the cyanide´s lethal effect
- lactate production, lactacidosis due to anaerobic glucose utilization

Symptoms

HCN (Zyklon B):
odour of bitter almonds, vertigo, confusion, convulsions, coma, “immediate” death

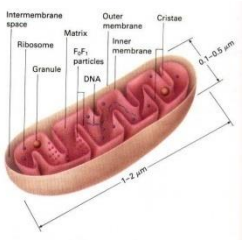
Cyanide salts: latency of 10-30 minutes – vertigo, nausea, vomiting, dyspnea, coma, death

Laboratory:

- lactacidosis
- arterialisation of venous blood (no arterial venous oxygen difference, pink skin)
- blood cyanide and thiocyanate levels
- **Biotransformation**:
- Rhodanese (thiosulphate sulphur transferase) is able to convert cyanide (-CN) with sulphur to thiocyanate (-SCN), excreted in urine

Two- phase therapy: I.phase (rapid):
(cheap)

- **Terapeutic methemoglobinaemia** (cyanide has a higher affinity for metHb (Fe^{3+}) and is released from cytochromoxidase (Fe^{3+})
- cyanide binds to metHb, leaves cytochromoxidase and then is slowly metabolised to thiocyanate and excreted in urine.



- Risky when metHb is higher than 30%!
- Cannot be used for HCN intoxication due to fire!!

ANTIDOTES – 1 phase METHEMOGLOBINIZING

Poppers

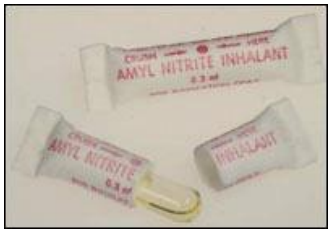
Amyl Nitrite Inhalant

JAC (James Alexander Corporation, USA)

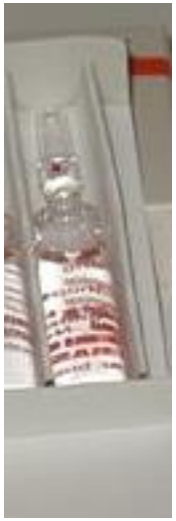
FIRST AID – 1-3 broken ampules

AT WORKPLACE!

no available



amylnitrite, butylnitrite, isobutylnitrite



\+

sodium nitrite inj. or

4-dimethylaminophenol (4-DMAP) inj.

i.v. TREATMENT –

by physician

Two- phase therapy: I.phase (rapid and safe):

B **Hydroxy**cobalamine inj. (forming of cyano**cobalamine** B_{12}) – antidote of choice

–very safe, no risk

– suitable for combustion gases (smoke HCN+CO)

–higher price

Two- phase therapy: II.phase: Na thiosulphate

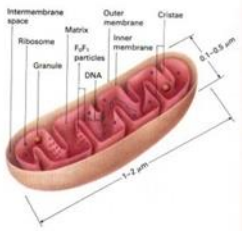
- **Sodium thiosulfate** (Natrium thiosulfate) – sulphur donor
- to excrete SCN into urine
- safe therapy

CARBON MONOXIDE - 1

- **Exposure:** automobile mechanics, fire fighters, superficial mines with brown coal - all incomplete combustion of carbonaceous material

Pathogenesis

- CO binds to Hb forming COHb which decreases
- hemoglobin oxygen saturation,
- shifts the **oxygen hemoglobin dissociation curve to the left,**
- increases the stability of Hb-oxygen combination, **thus inhibiting oxygen delivery to the tissues**,
- CO binds to cytochrome oxidase chain and interferes with cellular respiration.



CARBON MONOXIDE

Canary a a warning of the miners

- Affinity of Hb for CO is 210 times greater than that for oxygen.
- Because of 21% concentration of oxygen already 0.1 % CO in the air forms 50% COHb level in blood.
- Lighter than the air, concentrates in the upper part of the atmosphere
- COHb bond is reversible, half-life in room air is about 4 hours.

CARBON MONOXIDE

- about 1 % COHb in non-smokers
- 5-10 % smokers - impaired concentration
- 20 % headache, vertigo
- 30 % nausea, vomiting, impaired judgement
- 40-50 % syncope, coma, convulsions, angina
- 60 % cerebral edema, death

- *(light colour of the COHb- reddish skin,*
- *conservation of meat in CO atmosphere)*

CARBON MONOXIDE

- **Laboratory**: COHb in blood as soon as possible (recording of time)
- arterial blood gases (metabolic acidosis), ECG

- **Treatment**: removal from exposure
- oxygen with mask (half-life 1 hour)
- hyperbaric oxygen where available (half-life 20 min), esp. for pregnant women
- (foetus is more sensitive to CO)

Consequences

- **Chronic occupational intoxication** not described – reversible bond

- **Delayed CNS sequels (shortly after severe intoxication, long latency speaks against CO as a cause):**
- pseudoneurasthenic syndrome, extrapyramidal symptoms