Tsüaniidimürgistus:

mandlilõhnaline nähtamatu surm

Cyanide intoxication: Invisible death with a smell of almonds

V Erakorralise Meditsiini
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Case 1 : Cyanide ”worst scenario”

- Helsinki 10.23 am: code A7-5 (severe intoxication)
  - Paramedic unit H691 + MICU H190 w EMD on board
  - Rescue units: H25 (pioneer/chemical), H61 (fire engine), H63 (tank), P4 (fire chief)
- Industry hall on the outskirts of city
- Work mate calls: Male worker has ingested cyanide solution in suicide attempt, free fluids on the floor.
  - hall evacuated on orders of dispatching center.

Case 1-2 : Cyanide

- 11min : H61 + H691 first on scene;
  - on orders of P4 & EMD isolates building, no enter-order
  - through window a male is seen convulsing on the floor
  - several chemical canisters around, no smoke, no fluids seen.
- EMD & paramedics prepare iv sets, oxygen, antidote & stand by

- 18 min : H25 arrives w. Chemical suits -> building entered, patient seen 27 min from call
  - through filters no scent, no observation
  - patient lifeless in asystolic arrest, no superficial trauma, froth in mouth.
  - declared dead on scene. HazMat team clears building

- Suicide letter found & small opened bottle with solvent solution containing hydrogen cyanide. Up to 50 ml missing
- Forensic : cyanide intoxication.

Case 2 : West Virginia, USA

” Two firefighters die in blaze

By Jackie Ayres The Register-Herald Fri Feb 20, 2009, 11:45 PM EST
CRAIGSVILLE — Two volunteer firefighters lost their lives fighting a structure fire in the Cottle area of Nicholas County late Thursday night.

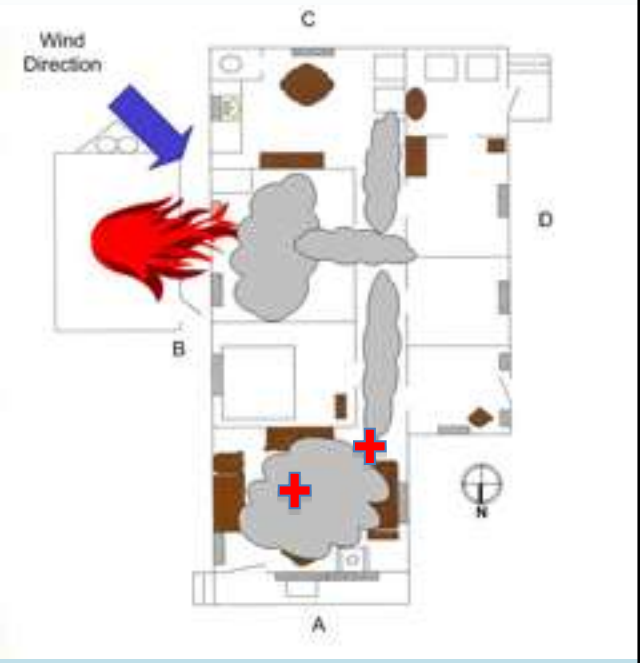
Lt. Johnnie Howard Hammons, 49, and firefighter Timothy Allen Nicholas, 26, both of Craigsville, died just after 10 p.m. at a mobile home just off W.Va. 20 in Cottle, according to Craigsville-Beaver-Cottle Fire Chief Tim Blake.
Hammons had been with the CBC Volunteer Fire Department 11 years. Nicholas had served one year. ”

Fire-fighters in to look for possible victims, after 10-15 min no reply to pump empty-alarm, hose out empty, no answer
Search found both lifeless inside smoke-filled building.
CPR without result.

Case 2-2 : West Virginia

” The victims were also found with their Nomex® hoods rolled down on their necks, without their facepieces on, and without a stand-alone or integrated PASS device.”

http://www.cdc.gov/niosh/fire/reports/face200907.html



- According to the medical examiner’s office, the victims died from smoke inhalation and thermal inhalation.
- The c**arboxyhemoglobin** (carbon monoxide poisoning) levels **were 63%** in Victim #1 **and 64%** in Victim #2. The toxicology reports for both victims showed **lethal doses of cyanide** in their systems.

Cyanide (CN)

Carbon-Nitrogen ion

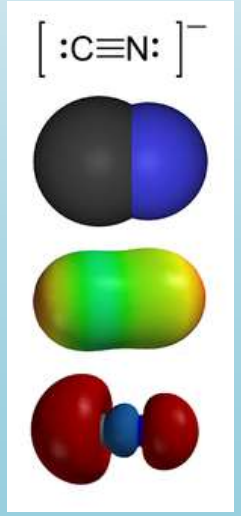
- Physiologic activities;
  - toxic when dissolved in body water
  - erythrocytes, tissues / plasma 10-100/1, 60% protein bound
  - affinite for metals

- Measurement a problem:
  - fast to intracellular space, metabolism, unstable in plasma, antidotes make measurement unreliable

! Very toxic;

- symptomatic plasma concentration > 40 µmol/
  > 0,5 mg/l

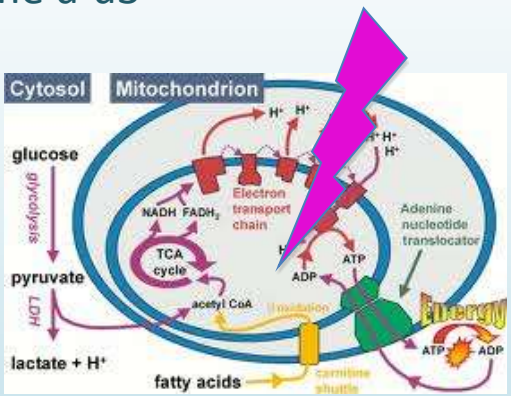
- lethal >100-300 µmol/l / > 1-2 mg/l



http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=72&tid=19
http://www.inchem.org/documents/antidote/antidote/ant02.htm

Toxicity

- Stops electron chain in mitochondrias
  - Binds competitively to the Fe3+-ion of cytochrome a-a3
  - Stops oxygen use & ATP production
- -> severe cellular hypoxemia



- Non-anaerobic tissue first down

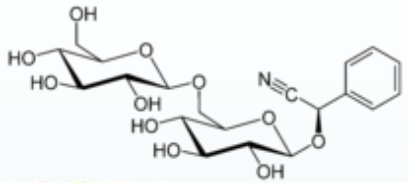
  = Brain, Heart

  -> anoxia symptoms, dyspnea

  -> CNS symptoms

  -> circulatory shock

Cyanide sources



- Organic glycosides = amygdalin
  - prunus-seeds: bitter almonds, apricot, prune, cherry
  - symptoms 1-10 hours after ingestion

- Salts
  - NaCN, KCN; 0.5-1.5mg/kg lethal, cases 200-250mg (adult) lethal
  - symptoms within 20min-2 hours after ingestion

- Liquid form : HCN (hydrogen cyanide, ”Prussic acid”)
  - very reactive, boiling point 25.6 C
  - absorbed through skin & mucous membranes (minutes-1 hr)
  - LD50 = 0.5mg/kg ; 60-90mg lethal (adult) … 1 tsp 2% solution
  - solvent in precious metals industry,
    in chemical industry compunds

Cyanide sources 2

- HCN : Gaseous form
  - lighter than air
  - almond smell not perceived by 5% -18% (genetic)
  - rapidly absorbed through lung surface
  - max permissive air concentration 10 ppm.. Immediately toxic 50 ppm, lethal 180 ppm / 10 min, 270 ppm / 5 min
  - set free from CN containing compounds when exposed to acid

  ! from pyrolysis of plastic, silk, wool, polyurethane, color pigment

Table 1. Hydrogen cyanide generated by pyrolysis

Material	µg HCN per g material
paper	1100
cotton	130
wool	6300
nylon	780
polyurethane foam	1200

From: Montgomery et al. (1975)

Intoxication : prevalence

- Oral / pure CN intoxications rare;
  - mostly suicide: industrial chemicals
  - inadvert: apricot seeds in children & ”natural remedies”

! Common : mixed intoxication from fire smoke

- Residential / industrial fire + exposure in closed space
- Synthetic textiles, plastic, isolation material
- Problem : no good way to measure concentration in field

Emergency care systems are the first
to encounter patients with major exposure !

Intoxication : clinical picture

- Hyper- to hypoventilation, vertigo
- Desorientation – agitation – **unconsciousness**
- Convulsions ?
- Arrhythmias..**Hypotension**..Circulatory shock

- **Mydriasis**
- **Blood lactate high early on**

! Symptoms are not specific

- lactate > 8-10 mmol/l is highly suggestive
  if no other obvious reason
- paradoxically high venous oxygen
- blood cyanide usually not available immediately

Fire : ”Smoke kills before heat”

! Fire smoke: Hot soot particles -> superficial burns, irritation

& Carbon monoxide -> CNS & circulatory symtoms, 20-30 min

& Cyanide -> Hypoxemia symtoms, 5-10 minutes

& Other irritant/toxic gases

-> mucous membrane irritation, bronchospasm 5-20 minutes,

-> lung reactions 6-24 hours

! Problems depend on concentration of toxins in smoke

.. and exposure time

- children, aged more prone to symtoms

- Smoke exposure + symtoms / death = CN exposure
- High CO correlates to high CN in blood
- Fire casualty with no burns, no CO have high CN

Baud, NEJM 1991; Grabowska 2004; Eckstein 2006 and others

Cyanide : diagnosis

1

- Exposure to cyanide or
- Exposure to CN containing chemicals / substances or
- Exposure to fire smoke in closed space
  - Smoke from plastic / isolation / wool / synthetic textiles = cyanide
  - Smoke in whole room = major exposure
  - > 10 minutes in smoke = major exposure
  - Soot in face/nostrils = major exposure & consider aiway burns too

+ 2

- In combination with general brain symptoms
- Especially if also hypotension and large pupils

= 3 ⇒ Treatment & Antidote is indicated

! First suspicion & decision to treat needs to be clinical

- blood CN usually not available immediately: final diagnosis & prognosis

Cyanide : Decontamination ?

- Not if only gas exposure

  - rescuers need positive pressure breathing apparatus (SCBA) in fires
  - chemical protection suits if free HCN

  ! Fire smoke : inhabitants out as early as possible

  - Rooms / areas above the fire are risky

- Surface exposure (liquid / solid) needs decontamination
  - Can cause intoxication by contact
  - Or release gas

    . temperature..acidity

Treatment: Intoxication

! In cyanide exposure / intoxication and fire smoke intoxication:

A) No symptoms / symtoms away spontaneously :

- **Inhalation : monitoring & oxygen**
- **Ingestion : activated charcoal & monitoring**
- -> transport to hospital follow-up
- -> antidote if symptoms

B) Symptoms :

- **Oxygen**, (though no proven effect on CN)
- **Advanced life support** with normal protocols **/ CPR**
- & **antidote as early as possibly (within 2 hours)**
- -> transport to intensive care when primary stabilization done

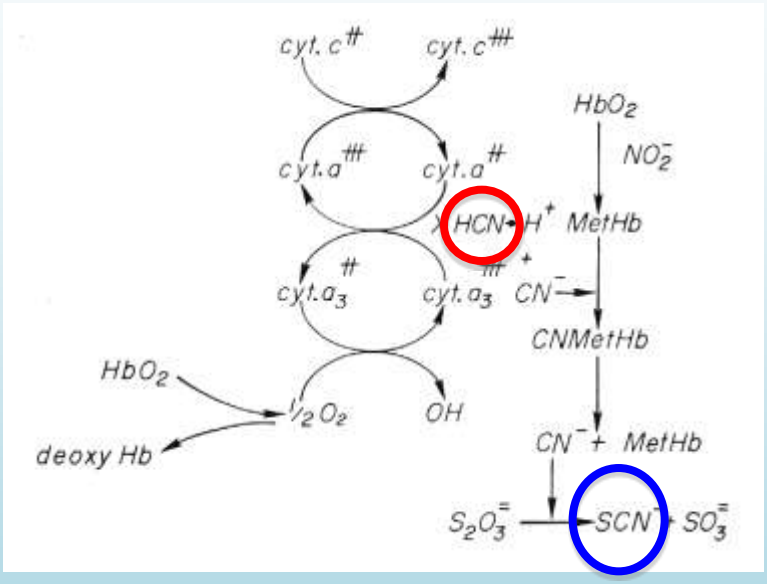
- **European guidelines:** Spain- Duenas-Laita: Emergencias 2010; France – Lapostolle: La Revue des SAMU 2010; Germany – Zilker, Der Notarzt 2010; Finland – Salmenperä: Duodecim 2004

Cyanide metabolism

- Main pathway (80%):
  - MetHemoglobin binds
  - Enzyme rhodanese adds sulphur
  - -> thiocyanate (SCN)

    -> excretion in urine
  - 0,017 mg/kg/h..

  ! High concentration of thiocyanate is also toxic



- Needs sulfur / cysteine
- Hemodialysis & -perfusion : no effect on CN

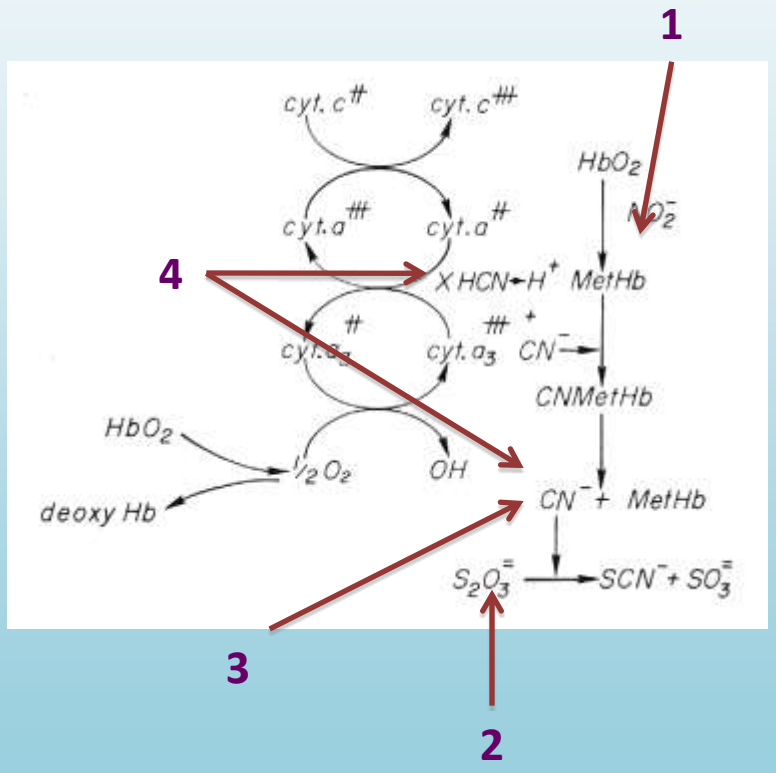
  - clears thiocyanate, ”slow” treatment

Cyanide metabolism & antidotes

1) Methemoglobinemia inducing agents
   - more MetHb = more CN out of mitochondriae

2) Sulphate substrate donors
   - more conversion to atoxic SCN

3) Chelating agents
   - chelates CN
   - binds CN to atoxic compound



Antidotes: Methemoglobin inducers

Fast .. but side effects : major methemoglobinemia (>60-70% lethal)

- Methemoglobinemia -> less oxygenation, bad if also CO-intoxication
- Antagonist : Methylene blue.. does not work if G6P-deficiency

- 4DMAP (4-dimethylaminophenol) 250 mg / 3-4mg/kg

  - iv -> in 1 min 35%-50% MetHb,
  - hypoxemia?, risk for hemolysis (G6P-deficiency!)

- Amylnitrite inhalation 0,2-0,4ml

  - 7% MetHb in 1-5 min
  - vasodilation: hypotension

- Sodium nitrite 10ml 3% infusion (300mg)

  - as amylnitrite
  - hypotension

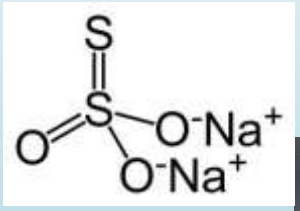
Antidotes : Sulphate donors

Slow, but few side effects

- helps physiologic excretion of CN

- Sodium thiosulfate 50ml 25% solution / 10 min iv
  - cheap
  - nontoxic (nausea, vomiting)

- 3-Mercaptopyruvate prodrugs
  - other sulphur pathway
  - on test stage only



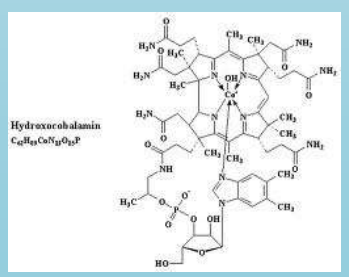
$$HSCH_2COCOO^- + CN^- \rightarrow CH_3COCOO^- + CNS^- .(1)$$

Antidotes : Chelating agents

Fast.. EDTA toxic, OHCob non-toxic

- Dicobolt-EDTA 300mg iv
  - Toxic: hypo/hypertension, ventricular arrytmia, anaphylaxia, voimiting
  - More if no CN = not on suspicion only
  - Only serum CN
  - glucose lessens toxicity & antidotal in itself ?..animal study
- Hydroxycobalamine

  - B-vitamin derivative, 5g iv binds 100-150 mg CN
  - binds (intra- &) extracellular CN -> soluble non-toxic complex
  - few side effects: red pigmentation of urine / skin, reversible skin reactions
  - disturbs some laboratory tests & co-oximetry (CO ⇧)
  - lessens thiosulphate effect ?



Comparing the antidotes

Antidote	Safety studies on humans	Shown effect in humans	Action	Serious AE:s	Clinical studies
Nitrites	Yes - severe adverse effects	Patient cases	Fast	Yes	No
4DMAP	No-too toxic	Pt cases	Fast	Yes	No
EDTA-Co2	No –too toxic	Pt cases	Fast	Yes	No
Thiosulphate	Yes	Pt cases	Slow	No	No
OH-Cobalamine	Yes	Patient series	Fast	No	Barron 2007

Intoxication : outcome

- Pure cyanide
  - if alive to antidote, >90% survival
  - positive publishing bias in case reports ?
  - no matched groups / patients series

- Fire smoke intoxication & toxic / lethal cyanide

  - lethal to twice or more lethal level of CN in blood, including resuscitated
    . 50% survival, in-hospital death due mostly to decortication
    . in non-resuscitated neurological signs disappeared in 58% after antidote
    . all-over survival from toxic cyanide 67% with antidote

Borron S et al. Prospective study of hydroxycobalamin for acute cyanide poisoning in smoke inhalation. Ann Emerg Med 2007

Take home message

! Remember cyanide

- nature remedies, plant parts, chemical workers suicide
- **fire smoke intoxication**

! Always suspect cyanide as well as CO in fire victims if:

- **central nervous system symptoms**
- **circulatory shock / cardiac arrest**
- high lactate

! Start treatment in the field

- **O2 & antidote & monitoring** & intensive care

! Get cyanide antidotes into emergency rooms & ambulances

- especially for fire smoke victims .. and firefighters

! Antidotes:

- methemoglobin inducers not good in smoke victims
- **cobalamine safe**
- **thiosulphate safe**, recommended as second line (with nitrites)

Thank You

Questions ?