
Methanol: first associations of clinical toxicologists

UK

USA

Norway

France

Czech Republic

Czech mass methanol outbreak: 138 cases, 52 deaths

Population:
10.5 mil.
Capital:
Prague – 1,25 m
Beers:
Pilsner Urquell,
Budweiser Budvar,
Kozel, Gambrinus

Drinks for the courageous men only:
Rum „Tuzemsky“, Plum vodka „Slivovitz“

Fomepizole versus ethanol in a mass methanol poisoning: The issue of comfort or „lege artis“?

- Fomepizole is included in WHO 18th Model List of Essential Medicines 2014 (20.2.2014).
- If hospital treatment with ethanol is still acceptable?
Methanol: perverted associations

You can almost smell the freshly cut grass!
Role of methanol in life

- **Atmosphere**: 1000 000 tons (3rd most abundant volatile organic compound)
- **Plants**: emission of up to 100 mg/kg FW/hour of MetOH (t ½ ~10 days)
- Signaling molecule in the intra- and interplant communication („alarm“)
- Fruit ripening (PME activity, CW degrading enzymes)
- „Plant-to-animal“ cross-kingdom signaling
- **Animals**: „methanol-responsive genes“ in the brain, modulation of gene expression, odor attractant for mammalians
Methanol in human metabolism

- Serum MetOH up to 5.5 mg/L
- Urine MetOH up to 7 mg/L
- **Exogenous sources:**
  - Plant Food, Fruits, Vegetables (Blanching)
  - Alcoholic Beverages (up to 7 g/L of 100% EtOH, USA)
  - Aspartame (ADI 40-50 mg/kg bw), 11% MetOH
- **Endogenous production:** 1.7 mg/kg/hour (3-4 g daily)
- Intestinal Microflora
- Demethylation (DNA, RNA, proteins, phospholipids) – **basic epigenetic mechanism**
Methanol: how we get rid of it?

- Non-metabolic clearance: <10% (urine 1 ml/min, breath 5-6 ml/min)
- Metabolic oxidation:
  - 90% oxidation leads to formaldehyde
  - 9% oxidation leads to formate
  - ROS formation: 60-70%
  - 10-20% formaldehyde in the brain
  - Serum formaldehyde: 0.1 mM
  - Brain formaldehyde: 0.2-0.4 mM
Formaldehyde: how we get rid of it?

- **Problems in the brain:**
  a) **FDH (ADH5)** – low $K_m < 0.01$ mM, easily saturated, glutathione-dependent
  b) **CYP450s** – ROS generation
  c) **ALDH1A1** (cytosolic), **ALDH2** (mitochondrial) – most important ($K_m 0.2-0.5$ mM): lower levels in neurons and astrocytes
Age-related neurodegeneration and brain formaldehyde

- Brain concentration of formaldehyde (FA) raises with age (A).
- Higher urine concentration of FA with age and in senile dementia (B).
- Increase of brain FA level reduces DNA/RNA methylation by inhibiting DNA methyltransferase (DNMT) activity and expression (C).
- Decline in DNA/RNA methylation, DNMT expression/activity with age (natural neurodegeneration), in AD (pathological neurodegeneration).
Pathological neurodegeneration and brain formaldehyde

- Higher brain and urine concentration of FA in Alzheimer‘s disease (D)

- Inhibition of DNMT and disruption of FA metabolism control in AD pathogenesis (E)

- Formaldehyde induces β-amyloid and tau protein aggregation, tau hyperphosphorylation, neuronal demyelinization (review by Tao Su et al, 2016)
Brain formaldehyde: increased external burden from 1981?

- Aspartam sweetener start from 1981
- Increase in US age adjusted AD death rate as aspartame consumption increases

Aspartic acid

OH  CO
\[\text{Aspartate} \quad \text{Phenylalanine} \]

\[\text{Methanol} \quad \text{Aspartame}\]
ALDH2: possible target for therapeutic interventions

• ALDH2 dysfunction (ALDH2*2 allele): risk factor for Alzheimer’s disease
• ALDH2: potent endogenous neuroprotective agent (4-HNE and other ROS-aldehydes scavenger)

• ALDH2 activators: new promising agents protecting heart against ischemia-reperfusion injury (*He L et al, 2012*)
• ALDH2 activators as brain stroke protectors (*Guo J-M et al, 2013*)
• ALDH2 activators: new anti-inflammation agents and pain-killers (*Mochly-Rosen D et al, 2014*)
ALDH2 Activators

- **ALDA-1 (ALdehyde Dehydrogenase Activator 1)** – 2-fold acceleration of the rate-limiting step in ALDH2 activity
- **ALA (alpha lipoic acid)** – well-known food supplement activating ALDH2
ALDH2 activation: more reliable and pleasant way…

- EtOH moderate administration activates ALDH2 and enhances 4-HNE, MDA and other ROS-aldehydes scavenging
- J- or U-shaped association with all-cause mortality
- Positive BAC at admission is associated with decreased odds of 30-day all-cause mortality in critically ill patients

Guo J-M et al, 2012

O'Keefe JH et al, 2016
CONCLUSION

• “Wine is one of the most civilized things in the world and one of the most natural things of the world that has been brought to the greatest perfection.”

• “Wine offers a greater range for enjoyment and appreciation than, possibly, any other purely sensory thing.”

• “Wine is the most healthful and most hygienic of beverages.”

• “At times we ought to drink even to intoxication for wine acts as a remedy to sorrow as it does to some diseases.”

• “The inventor of wine is called Liber because he liberates the mind from the bondage of cares and emancipates it, animates it and renders it more daring in all that it attempts.”
Thank you for attention