Acetaldehyde and gastric cancer Minimizing of acetaldehyde exposure

Mikko Salaspuro, prof., M.D., Ph.D., Research Unit on Acetaldehyde and Cancer, University of Helsinki, Helsinki, Finland

COI
Board member, medical adviser and stock owner of Biohit Oyj., Helsinki, Finland

Eesti Arstide Liidu
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mikko.salaspuro ätt helsinki.fi

Gastric cancer in Estonia (Globocan 2012)

- Still important health problem
  - 370 new cases annually
  - 6.0 % of all cancers
- Poor prognosis
  - Annual mortality is 286
  - 7.9 % of all cancer deaths
  - After lung and colorectum number 3 in cancer mortality
- Both operative and medicinal treatment are challenging
- Expenses at a population level are marked
- Psychic and physical suffering “no-hope feeling” is common
- Main focus should be on the prevention

A key to cancer prevention

- Identification of specific etiologic factors and/or carcinogenic compounds
- Examples of specific human group 1 carcinogens
  - Asbestos, formaldehyde, benzene, tobacco, radon
- The use of each of them is strictly regulated by internationally accepted laws
  - These directives have been shown to be effective in cancer prevention both at a population and individual level

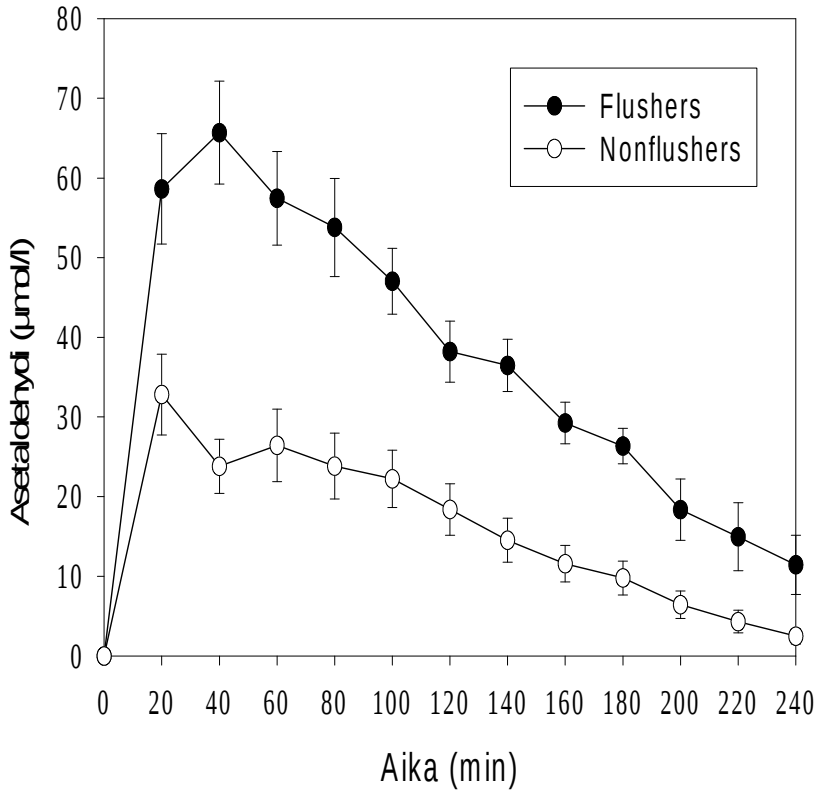
Carcinogenicity of acetaldehyde is based on a unique human cancer model

- ALDH2-enzyme is responsible for the very effective elimination of acetaldehyde formed from ethanol in somatic cells
  - 100% of acetaldehyde is eliminated in the liver
- A point mutation in ALDH2-enzyme gene results in markedly decreased ALDH2-activity
- Mutation has randomized tens of thousands of alcohol drinking East-Asians for decades to markedly increased local exposure to acetaldehyde
- This associates with markedly increased risk for upper digestive tract cancer

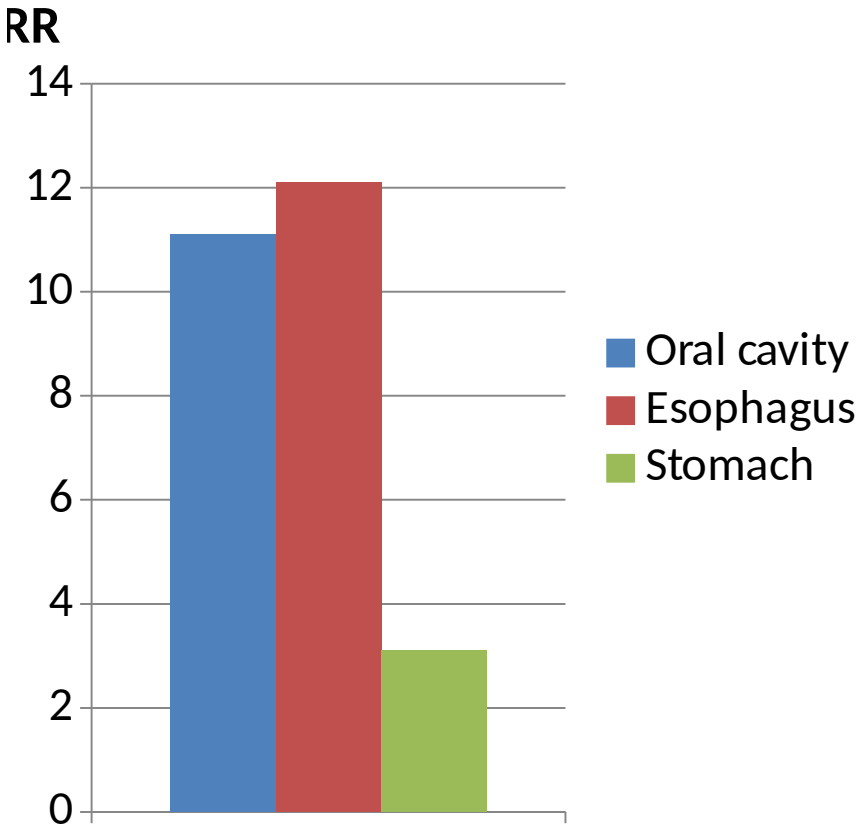
Comparable human model is not available for any other of the 113 human group 1 carcinogens

ALDH2-deficiency – a unique human cancer model

Salivary acetaldehyde after 3 doses (0.5g/kg) of alcohol in ALDH2-def.



Relative risks (RR) of upper digestive tract cancers in ALDH2-deficient heavy drinkers vs. heavy drinkers with active enzyme



Yokoyama et al. Carcinogen 1998;19:1383-7

Characteristics of ALDH2-deficiency

- Affects over 500 million East-Asians
- In homozygotes ALDH2 enzyme is undetectable
  - Protects from alcoholism because of severe flushing reaction associating with alcohol drinking
  - In a few smoking alcoholics esophageal cancer risk is up to 400-fold compared to never drinkers/-smokers without mutation
- In heterozygotes less than half of the enzyme activity is detectable in most somatic cells
  - Less severe flushing reaction
  - May become heavy drinkers and alcoholics
  - ➢ Markedly elevated (2.5 – 5.6-fold) acetaldehyde concentrations in the saliva and gastric juice after drinking of alcohol
  - ➢ Markedly increased upper digestive tract cancer risk

ACETALDEHYDE I

Most widespread human carcinogen

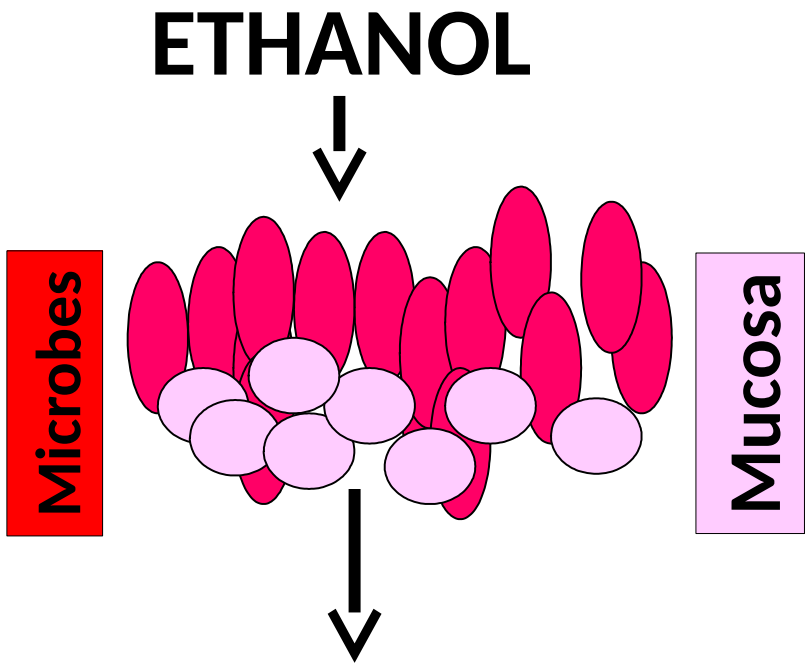
- In most alcoholic beverages and food stuffs produced or preserved by fermentation
- Used widely as an aroma agent and food additive
- Most abundant carcinogen of tobacco smoke
- Carcinogenicity associated with the use of alcoholic beverages is mediated via acetaldehyde. This concerns:
  1. Free acetaldehyde present in alcoholic beverages
  2. Free acetaldehyde formed from the oxidation of ethanol locally in the upper digestive tract by normal microbial flora and mucosal cells

ACETALDEHYDE II

- Acetaldehyde is carcinogenic to animals
- International Agency for Research on Cancer (IARC)
  - Acetaldehyde associated with alcoholic beverages is carcinogenic to humans (Group 1)
  - A causal relationship between alcohol associated acetaldehyde and upper digestive tract cancers has been demonstrated in gene-epidemiological and biochemical studies
- Apple or orange flavor
- Boiling point = 20,2 ^{o}C
- Water and lipid soluble
  - Passes without difficulty through cell membranes

Accumulation of acetaldehyde in saliva and gastric juice

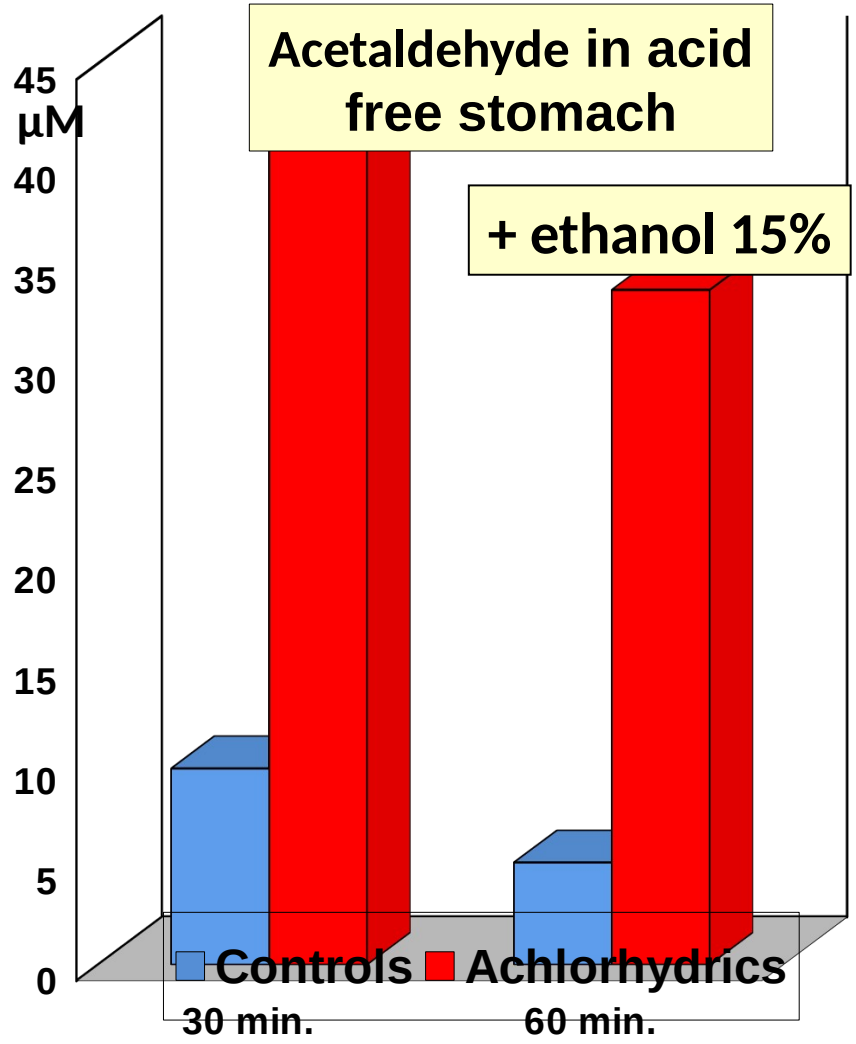
- Under 1 % of alcohol is metabolized locally to acetaldehyde by microbes and mucosa
- Microbes and mucosa have a low capacity to metabolize acetaldehyde
- Highest acetaldehyde concentrations after alcohol intake are found in saliva and gastric juice



ACETALDEHYDE
in saliva and gastric juice

Acetaldehyde in gastric juice

- Atrophic gastritis is a major risk factor for stomach cancer
- According to a recent meta-analysis also the use of gastric acid secretion inhibitors increase the risk for gastric cancer
- Both conditions are characterized by hypochlorhydria or acid free stomach in which oral microbes are able to survive and multiply
- Many of those microbes possess ADH enzyme and produce effectively acetaldehyde from any ethanol
- Glucose may also serve as a substrate for acetaldehyde production



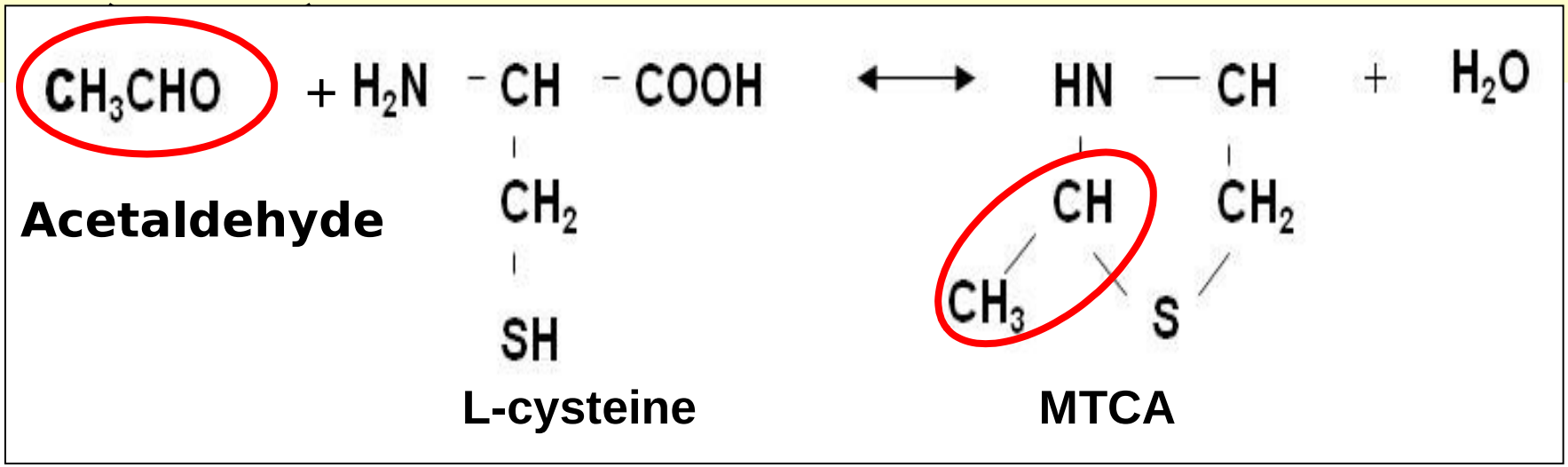
Väkeväinen et al.
Scand J Gastroenterol 2002;37:648-55

Minimizing acetaldehyde exposure

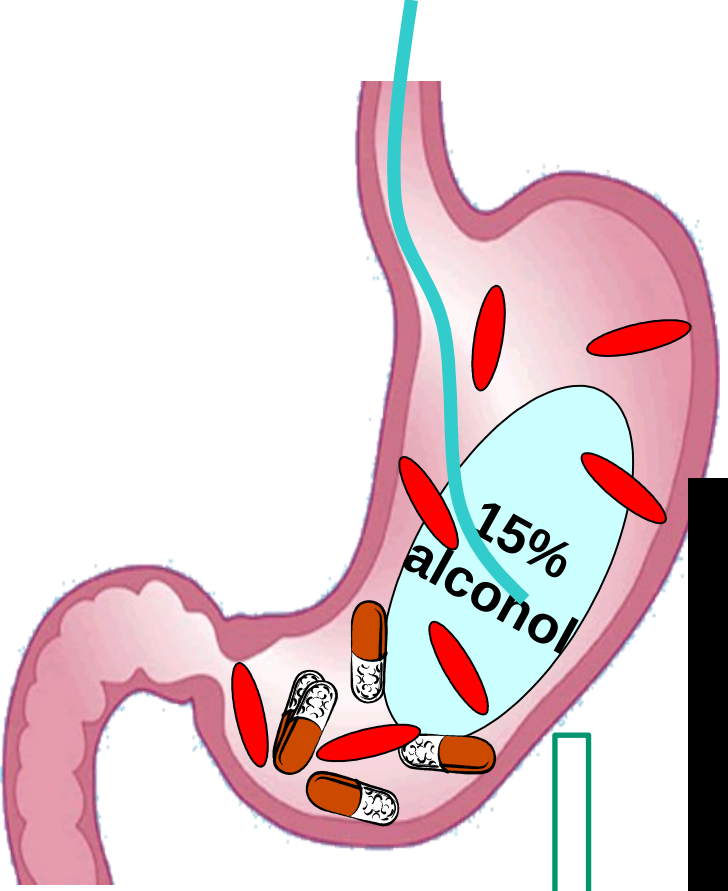
- Exposure to acetaldehyde can be markedly minimized by many ways both at a population and individual level
  - Quitting from smoking
  - Moderation in alcohol consumption
  - Avoiding beverages and food stuffs containing acetaldehyde and/or alcohol
- Slowly L-cysteine releasing capsule (Acetium)
  - A novel approach
  - Binds and inactivates 60 -70% of intragastric acetaldehyde after alcohol intake

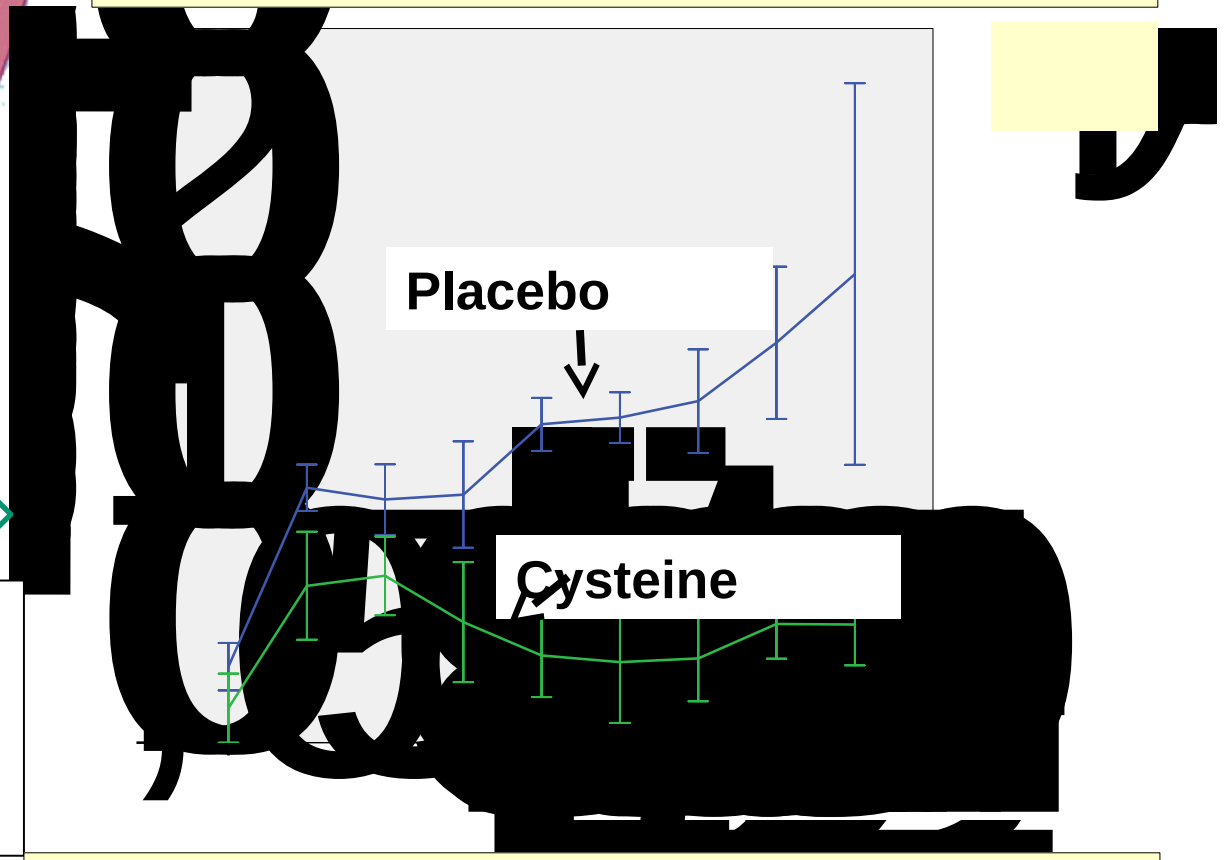
L-CYSTEINE

- Semi-essential sulphur containing amino acid
- Mean daily intake is 1 - 2 g
- Binds covalently and non-enzymatically to acetaldehyde and forms
  - inactive methyltiazolidinecarboxylicacid



L-cysteine (200mg) binds 60-70% of acetaldehyde in gastric juice after a dose of alcohol



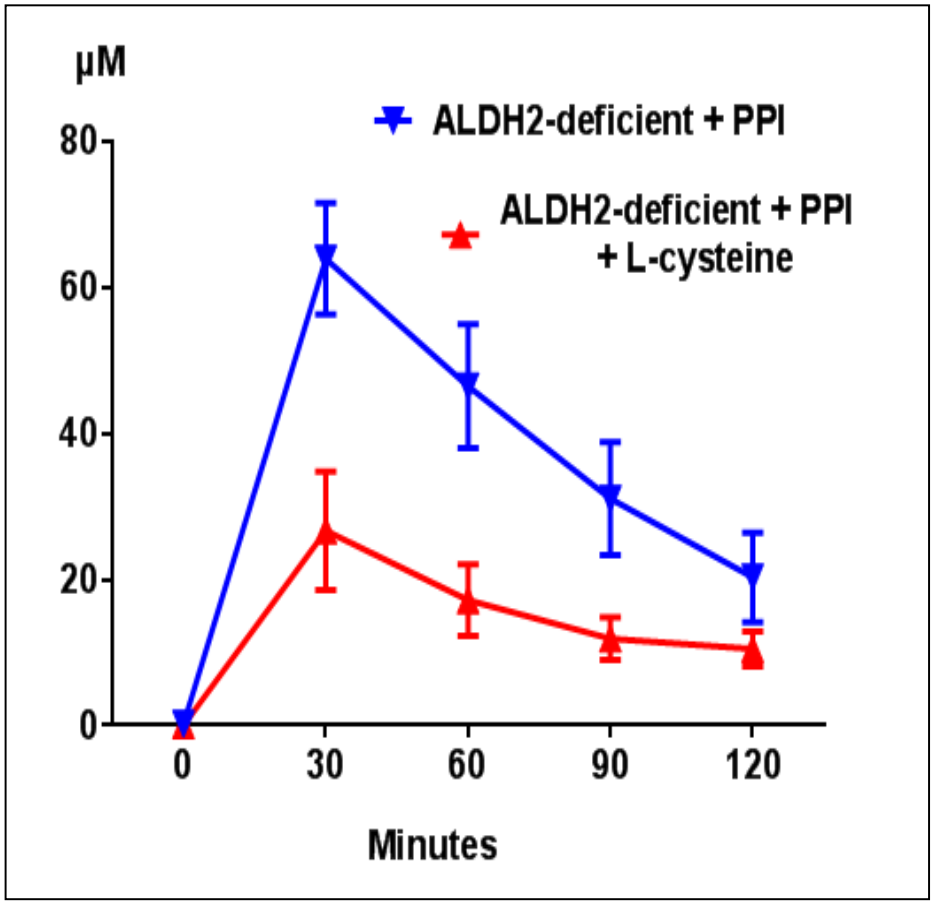


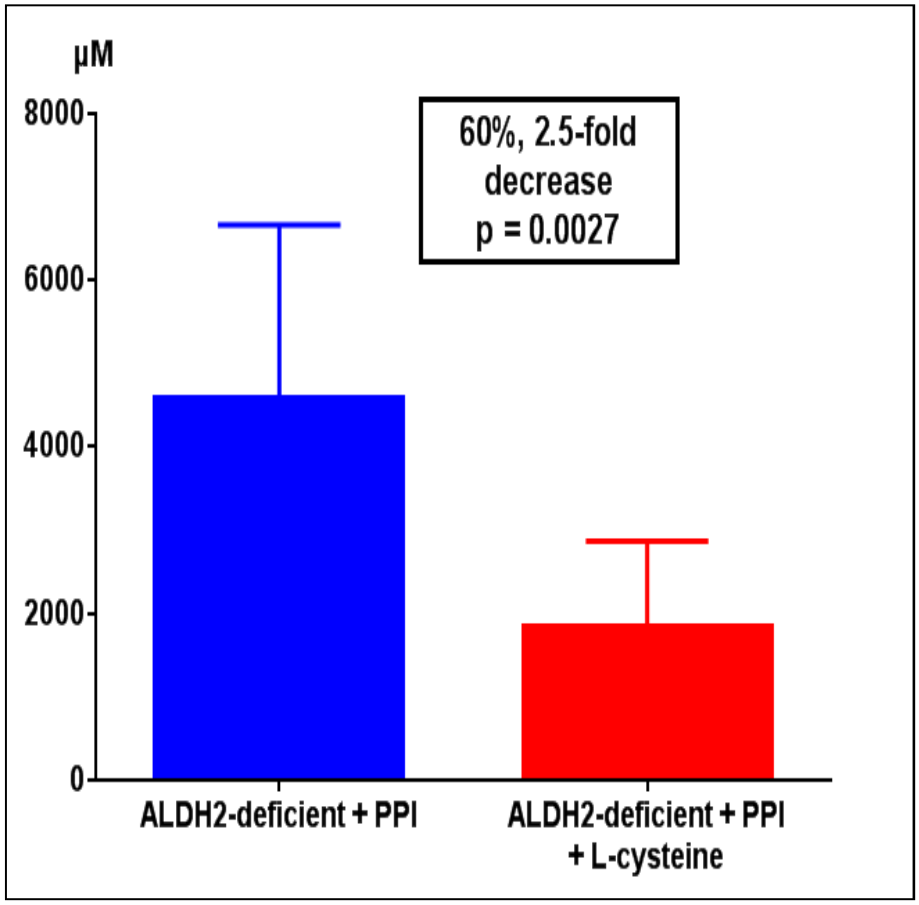
Achlorhydric stomach

- microbes
- L-cysteine capsules
- 15 % alcohol

Linderborg et al. Alcohol Clin Exp Med 2011;35:516-22

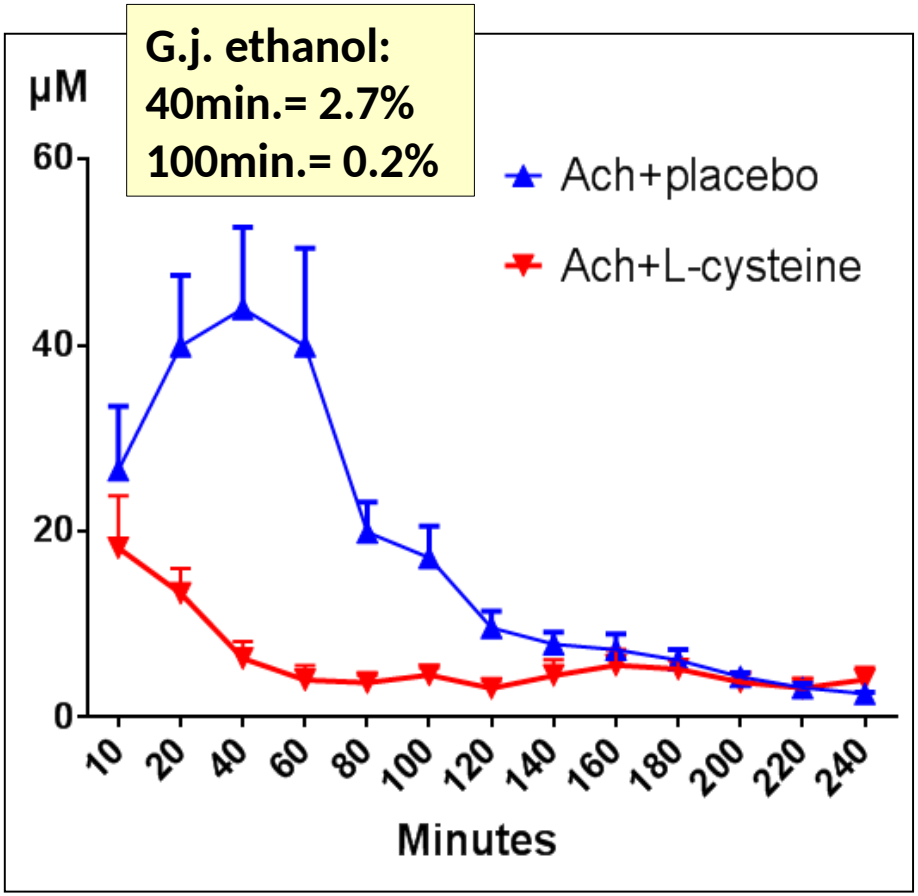
Effect of slowly L-cysteine releasing Acetium capsule on gastric juice acetaldehyde in PPI-treated ALDH2-deficients

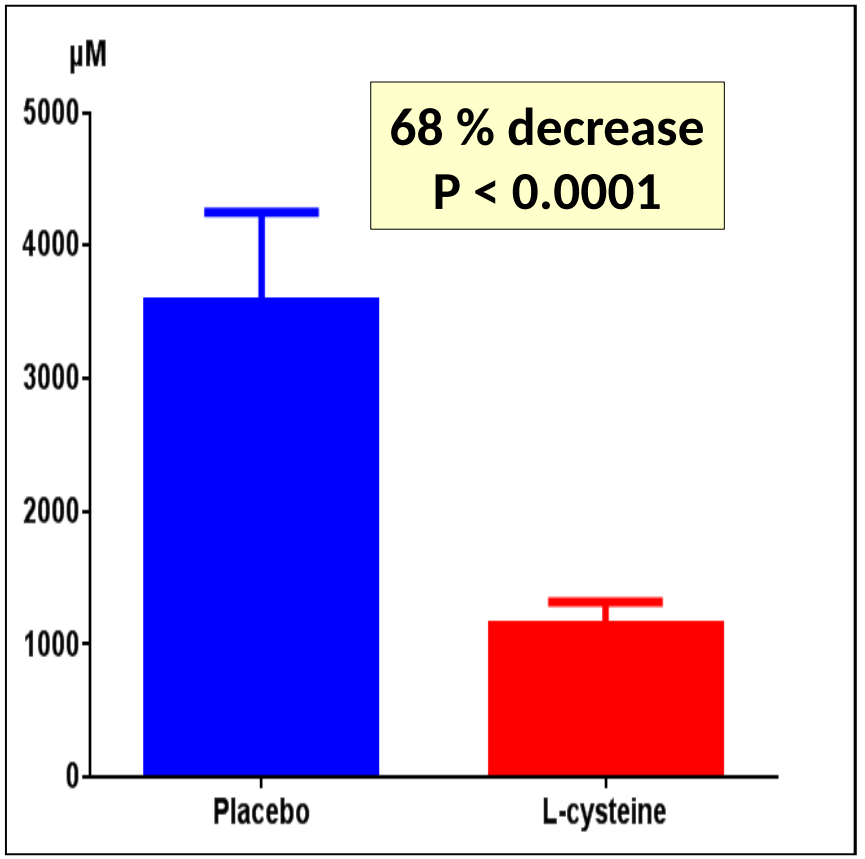




- Hypochlorhydria was produced by rabeprazole (10mg b.i.d., 7 days)(n = 10) ► Acetium capsules (L-cysteine 100mg x 2) ►intragastric infusion of 15% alcohol (0.5g/kg)
- Maejima et al. (Division of Gastroenterol., Tohoku Univ. Japan) PLOS ONE 2015, in press

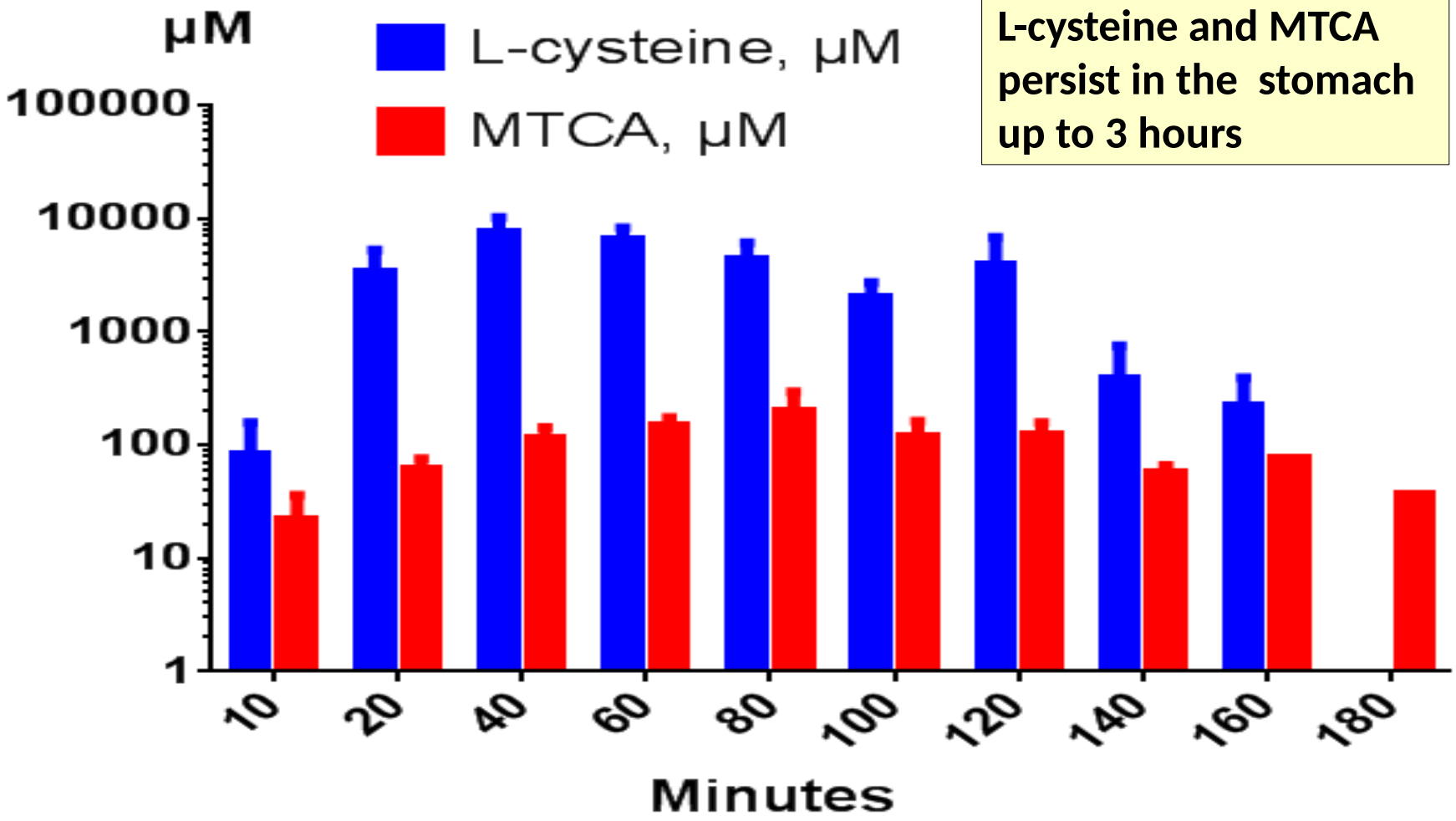
Effect of slowly L-cysteine releasing Acetium capsule on gastric juice acetaldehyde





- Patients with atrophic gastritis (n = 7) ►ethanol (15%) 0.3g/kg ►L-cysteine (100mg x 2) or placebo, gastric juice ethanol, acetaldehyde, L-cysteine and MTCA levels for 4 hours
- Hellström PM et al. (Department of Med Sci, Uppsala), DDW 2014

Effect of slowly L-cysteine releasing Acetium capsule on gastric juice L-cysteine and MTCA



L-cysteine and MTCA persist in the stomach up to 3 hours

Hellström PM et al. (Department of Med Sci, Uppsala), DDW 2014

ACETIUM capsule

A novel innovation

- **L-cysteine (100mg) is released slowly in the stomach where also acetaldehyde is formed**
- **To those with acid free stomach (indications)**
  - **Atrophic gastritis**
  - **Use of PPI-drugs**
  - **Operated stomach**
  - **Chronic *Helicobacter pylori* infection (*H.pylori possess ADH)***

CONLUSIONS

- Carcinogenicity of acetaldehyde is based on a unique genetic human model
- Acetaldehyde is the most prevalent human carcinogen
- Atrophic gastritis resulting in hypochlorhydric or acid free stomach is the most important risk factor for stomach cancer
- Acid free stomach is colonized by oral microbes producing mutagenic concentrations of acetaldehyde from any ethanol in the stomach and also from glucose
- Slowly L-cysteine releasing Acetium Capsule (2 x 100mg of L-cysteine) eliminates 60-70 % of gastric juice acetaldehyde after alcohol drinking
- ACETIUM capsule is so far the only commercially available product for the local elimination of carcinogenic acetaldehyde in the stomach


Thank you for your attention