2016 Joint Conference of Poison Control Centres

Evaluation and Management of Seriously Ill Poisoned Patients

Toxic Alcohols Poisoning

Dr. Jones C.M. Chan
Associate Consultant
Prince of Wales Hospital Poison Treatment Centre,
and Division of Clinical Pharmacology
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

Content

- Cases of toxic alcohol poisoning
- Metabolic difference
- Diagnostic pitfalls
- Interpretation of osmolar gap (OG)
- ADH inhibition: fomepizole vs ethanol
- Fomepizole monotherapy?
- Elimination: Intermittent HD vs CVVHD/HDF

Case 1: Unanticipated source

- M/52 yo, history of Kennedy's disease (Motor neuron disease variant)
- Found unconscious by a bystander in a street, with strong thinner smell
- To AED 30 min later, GCS 9, BP 190/99, P 142 bpm, RR 30, SaO2 92% on 15 L O_2
- ECG – fast AF / SVT
- ABG – pH 7.09, PCO_2 5.5 kPa, PO_2 kPa, BE -18 mmol/L
- AG, OG not available on admission

- 8.5 h later, OG = 52 mOsm/kg, AG = 14 mmol/L
- Serum ethanol, salicylate, paracetamol –ve
- Serum methanol screening +ve
- Started HD and ethanol infusion, followed by CVVHD
- Serum methanol level 29 mmol/L

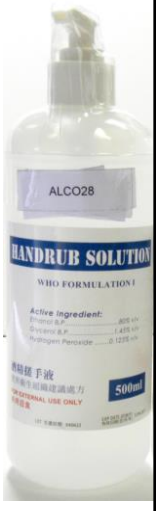
Case 2: Unexplained coma

- F/30 yo, chronic alcoholism, chronic pancreatitis, history of alcohol withdraw seizures

- Admitted to hospital for drunk, observed in the AED
- Initially GCS 14, developed coma suddenly on day1
- CT brain NAD, admitted to ward

- Developed second episode of coma suddenly (GCS 10) on day2
- CT brain NAD

- Developed third episode of coma suddenly (GCS 9) on day3
- Witnessed of drinking of bedside alcohol-based handrub by other patients before coma
- OG ~117.2 mOsm/kg, pH 7.3
- Serum ethanol level 127 mmol/L



Case 3: Alcohol handrub again!

- M/29 yo, intellectual disability, autism
- Recent admission for ingestion of handrub (surfactant-based)

- Admitted to hospital for ingestion of alcohol-based handrub
- To AED 1h later, GCS 3, BP 111/65, P 68 bpm, SaO2 82% on 15L O2
- ABG: pH 7.28, PCO_2 7.5 kPa, PO_2 10.2 kPa, BE -2 mmol/L
- Plasma lactate 3.7 mmol/L
- OG 129 mOsm/kg
- Serum ethanol <4.3 mmol/L

- Serum methanol screening test +ve
- Serum methanol level 72 mmol/L (on admission)
- Serum isopropanol level 55 mmol/L
- Serum acetone 12.9 mmol/L
- Treated with HD, ethanol and Ca folinic acid infusion, and followed by CVVHD

Listed ingredient: Isoproyl alcohol...
Isopak – methanol 22%, ethanol 3.5%, isopropanol 36%

Case 4: Methanol poisoning again?

- F/48, schizophrenia, ex-intravenous user, recurrent drug overdose

- Admitted to hospital for unwell for 2 days
- Impaired conscious level on admission, GCS 7, Hemastix >27 mmol/L
- ABG – pH 6.72, PCO_2 1.58 pKa, PO_2 19.3 kPa, BE -34 mmol/L, plasma glucose 49 mmol/L
- Serum ethanol, salicylate -ve
- Treated as DKA with insulin and fluid resuscitation

- 3h later
- ABG – pH 6.9, PCO_2 2.0 pKa, PO_2 16 kPa, BE -28 mmol/L
- OG 30.5 mOsm/kg, AG 37 mmol/L

- 9h later
- ABG – pH 7.16, PCO_2 3.6 kPa, 10.9 kPa, BE -18 mmol/L
- Serum methanol screening test +ve
- Started CVVHD and ethanol infusion
- Developed hypotension after ethanol loading
- Changed to IV fomepizole

- Plasma methanol confirmation test -ve

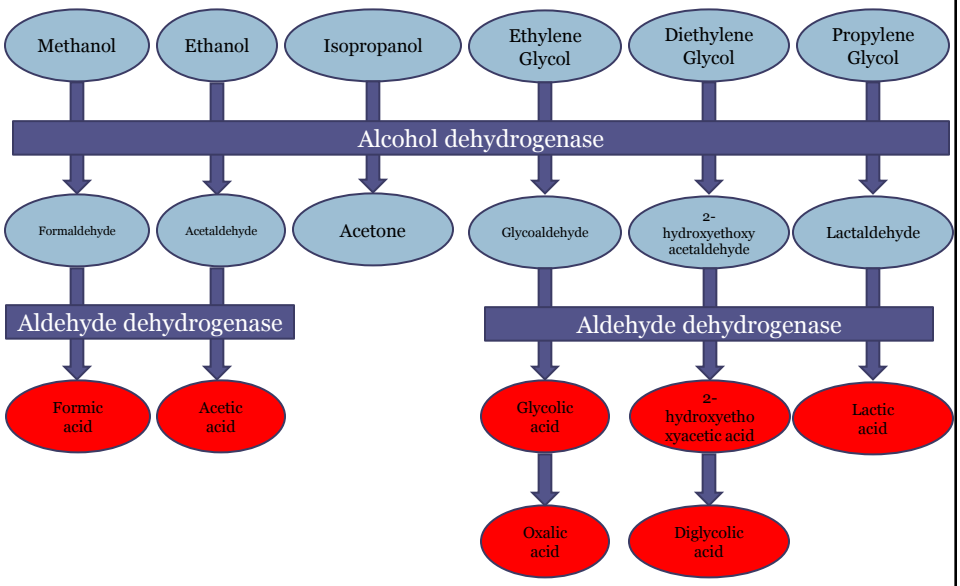
Challenge in management of toxic alcohol poisoning

- Early diagnosis
  - Unanticipated source of toxic alcohol
  - Comatose patient who provides no history
  - Non-specific symptoms and signs of poisoning
  - Delay onset of toxicity when ethanol is co-ingested
  - Limitations in laboratory tests
- Effective treatment
  - ADH inhibition (Fomepizole vs ethanol)
  - Role of haemodialysis

Alcohol: R-OH
Glycol: HO-R-R-OH

R-OH	Molecular formula	Molecular weight	Vod (L/Kg)
Methanol	CH3OH	32.04	0.6 – 0.7
Ethanol	CH3CH2OH	46.07	0.5
Isopropanol	CH3CHOHCH3	60.09	0.6-0.7
Ethylene glycol	$(HOCH)_2$	62.07	0.7-0.8
Propylene glycol	CH3CHOHCH2OH	76.09	0.5
Diethylene glycol	$(CH2CH2OH)_2O$	106.12	0.5

Metabolism of alcohol / glycol and acidosis



Unanticipated sources of toxic alcohol

General Use: Fuel, solvent, precursor to make polymers, antiseptics, dehydrating agents, humectant, screenwash, anti-freeze

R-OH	Unanticipated sources
Methanol	
Ethylene glycol	
Diethylene glycol	

Adapt from:
Application to include fomepizole on the WHO model list of essential medicines 2012

Symptoms and signs of acute poisoning may vary

CNS

- 0.5 – 4h:
- Transient inebriation, euphoria
- Isopropanol ≈ ethylene glycol > ethanol > methanol
- Less in chronic alcoholic who has tolerance

Acidosis

- 12 – 24h:
- Formation of toxic organic acids
- Kussmal breathing

End-organ damage

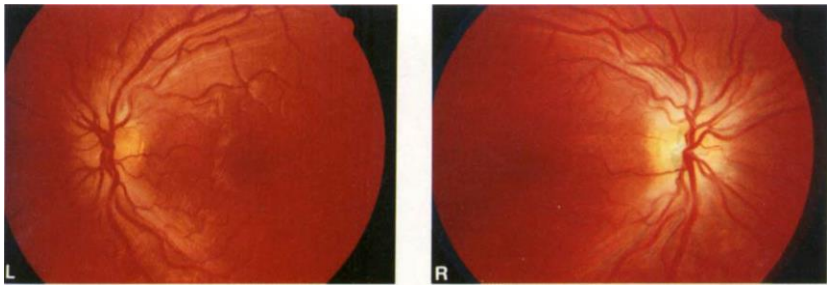
In Methanol

blurring of vision, defect in color vision and "snow field" in 50% of patients
Early signs: Reduced pupillary responses to light, optic disc hyperemia (which usually subsided within 3 days)
Late signs: retinal edema, central scotoma

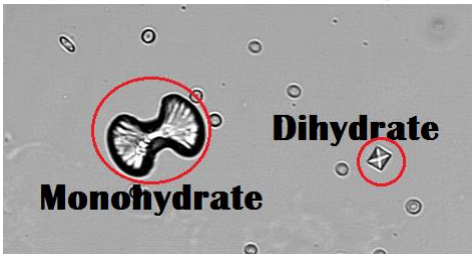
In Ethylene glycol

Formation of oxalic acid and hypoCa, calcium oxalate deposition in the meninges, blood vessels, myocardium, kidney tubules
seizures, coma, cerebral edema, vomiting
24 – 72h: oliguric renal failure, flank pain

Symptoms and signs of acute poisoning may vary



Stelmach MZ. Australian and New Zealand Journal of Ophthalmology 1992



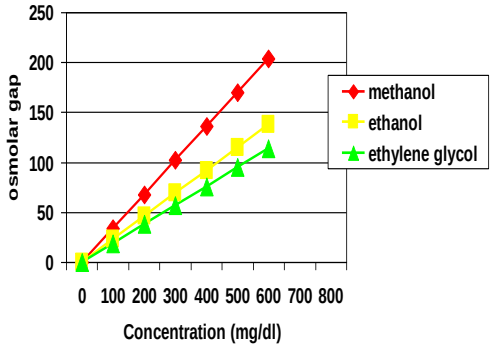
Delay onset in toxicity in co-ingestion

- In methanol poisoning, changes in mental states usually occur within 6 – 24 hr
- In co-ingestion of methanol and ethanol, there is a delay in onset of neurological symptoms for as long as 72 – 96 h.

Jacobsen D, McMartin KE. *Med Toxicol Adverse Drug Exp 1986;* 1: 309–34.
Hovda KE, et al. *J Intern Med 2005;* 258: 181–90.
Barceloux DG, et al. *J Toxicol Clin Toxicol 2002;* 40: 415–46
Hovda KE, et al. *Intensive Care Med 2004;* 30: 1842–6.
Bennett JL, et al. *Medicine 1953;* 32: 431–63.

OG and molecular weight of alcohols

	Molecular weight	ΔSOsm (mOsm/L) per 10 mg/dl Serum Alcohol Concentration
Methanol	32	3.09
Ethanol	46	2.12
Isopropanol	60	1.66
Ethylene glycol	62	1.6
Propylene glycol	76	1.31
Diethylene glycol	106	0.9

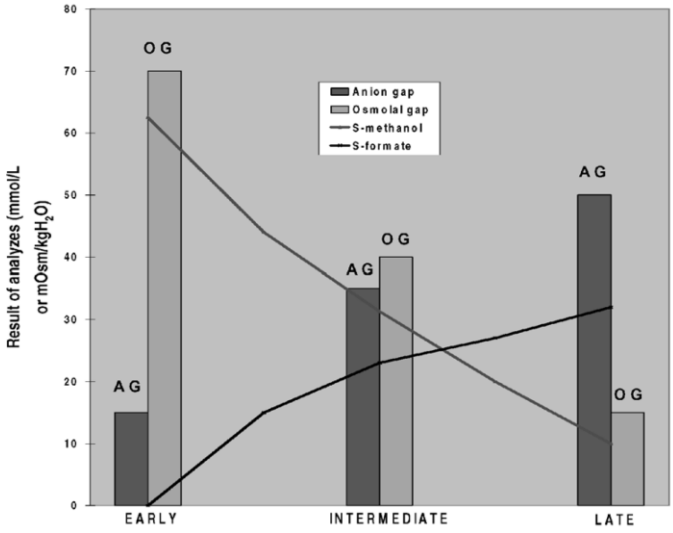


Serum toxic alcohol level (mg/dL) = CF* x Osmolar gap

CF* = 3.2 (methanol); 4.6 (ethanol); 6.0 (isopropanol); 6.2 (ethylene glycol)

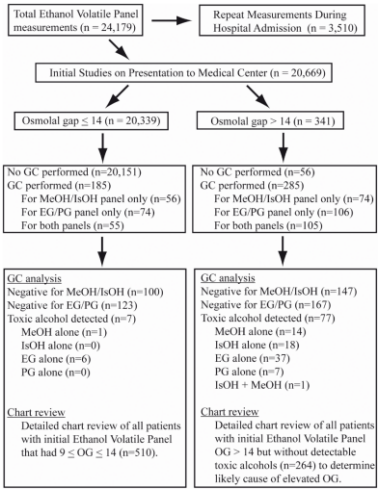
Adapted from:
Kraut JA, Kurtz I. Clin J Am Soc Nephrol 2008; 3: 208-25

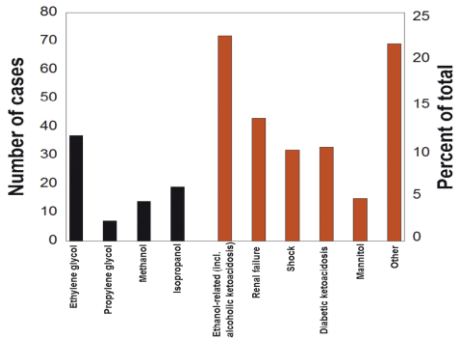
Changes in OG and AG with time



Hovda KE, Hunderi OH, Rudberg N, et al. Intensive Care Med. 2004 30(9): 1842-6

Diagnostic accuracy of the OG in screening for toxic alcohol ingestion





For OG 20 mOsm/kg
Sensitivity of 0.82; Specificity of 0.85 for dx of toxic alcohol ingestion
History is often helpful to identify the cause
Most non-toxic alcohol cases, OG < 30 mOsm/kg

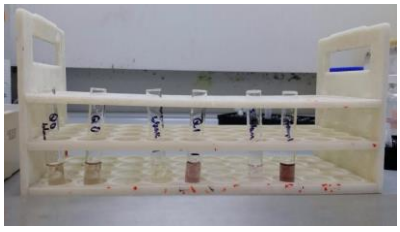
Krasowski MD, et al. BMC Clinical Pathology 2012; 12(1)

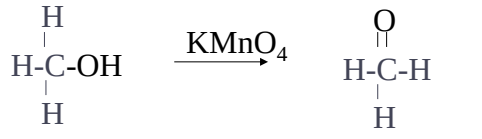
Usefulness of OG

- Normal OG = -14 to 10 mOsm/kg
- A moderately elevated OG (10 to 20 mOsm/kg) can occur in other causes other than toxic alcohol poisoning
- A significant elevated OG (>50 mOsm/kg) is highly suggestive of toxic alcohol poisoning
- A normal OG cannot exclude toxic alcohol poisoning

Screening and confirmatory tests

R-OH	Screening test	Quantitative
Methanol	Colorimetric	GC-FID
Ethanol	-	Spectrophotometry
Isopropanol	-	GC-FID
Ethylene glycol	LCMS (oxalate in urine)	GC-FID (glycolic acid)
Propylene glycol	-	GC-FID
Diethylene glycol	-	GC-FID





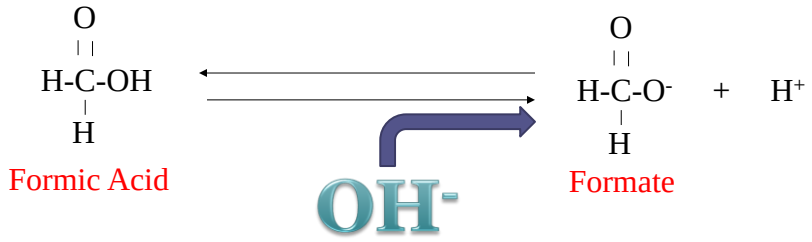
Methanol Formaldehyde

GC-FID: Gas chromatography-Flame ionisation detection
LCMS: Liquid chromatography mass spectrometry
24 hour available testing; No 24 hour available testing

Management overview

- Investigations:
  - RFT, glucose, Ca, ethanol, blood gas, Cl, lactate, β-hydroxybutyrate
  - Determine OG, AG
  - Urinalysis for oxalate crystals, urine fluorescence
  - Serum methanol, ethylene glycol, isopropanol
- Management:
  - ABC
  - Activated charcoal – not useful
  - Correction of metabolic acidosis
  - ADH inhibition
  - Haemodialysis
  - Thiamine / pyridoxine / Mg for EG
  - Folinic acid for methanol

Correction of acidosis



- Formic acid is three times more potent as an inhibitor of mitochondrial electron transport
- Further increase production of lactic acid and acidosis
- Increase formic acid toxicity to CNS
- Management: aim serum pH 7.35 – 7.45

ADH inhibition

	Fomepizole	Ethanol
Affinity to ADH	50-100 times > ethanol	20 times > methanol
Pharmacokinetics	Predictable Metabolised by Cyt P450 2E1, induction occurs after 48 h of administration	Erratic Elimination rate is higher in chronic alcoholism
Dosing regimen	Standardised and simpler	Complicated
Treatment monitoring	Not required	Monitoring in every 1-2 h, aim plasma ethanol ≈ 100 mg/dL (21.7 mmol/L)
Adjustment during HD	Shorter time interval	Higher rate of infusion
Adverse effects	Fewer, milder and transient	Common, CNS depression, hypoglycaemia, thrombophebitis
Cost	High	Low
Availability	Low	High
Efficacy	Shown to prevent metabolic acidosis and end-organ damages, FDA approved for EG (1997), and methanol (2000)	Used since 1940s, no prospective clinical trails Not FDA approved

Treatment criteria of fomepizole

AACT/EAPCCT Recommendations (1999; 2002)

Documented recent history of EG or methanol ingestion and OG >10 mOsm/kg

Hx of EG or methanol ingestion and ≥2 of the followings:

- Arterial pH <7.3
- Serum HCO_3 <20 mmol/L
- OG >10 mOsm/kg
- Urinary oxalate crystals present (for EG only)

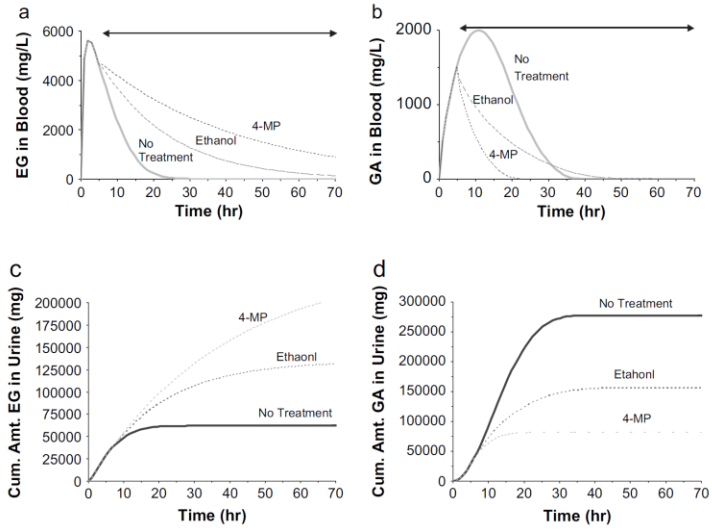
Serum EG or Methanol >20 mg/dL (nonacidotic)
(3.2 mmol/L for EG; 6.2 mmol/L for methanol)

-Methanol: pH <7.22 is a better predictor of mortality
-EG: pH is less useful (Goldfrank Toxicologic Emergencies 10th ed)

-Formic and glycolic acid levels – more correlate with toxicity

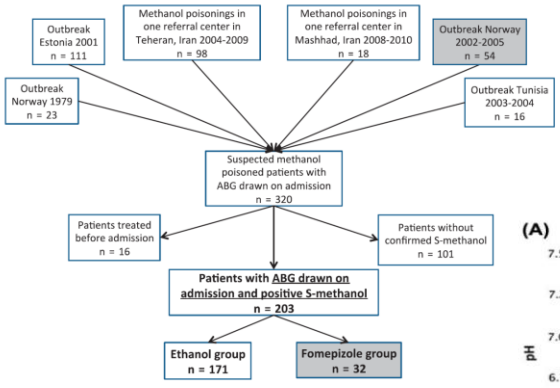
-Lack of correlation with clinical effects
-Insufficient data to support (Kostic MA 2003)

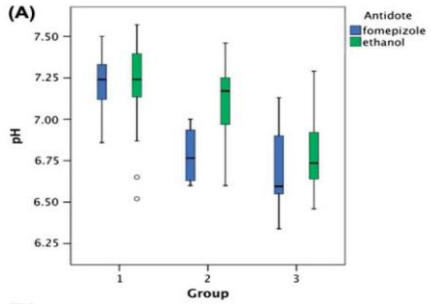
A simulation model Comparing fomepizole and ethanol in EG poisoning



Corley RA, McMartin KE. Toxicological Sciences 2005; 85: 491-501

Comparison of fomepizole and ethanol in Methanol poisoning





Gp 1: Survivors without sequelae (n = 121)
Gp 2: Survivors with sequelae (n = 34)
Gp 3: patients who died (n = 48)

Paasma R, et al. Clinical Toxicology 2012; 50: 823 – 831.

When to stop ADH inhibition?

- Fomepizole or ethanol can be stopped when:
  - Patient is asymptomatic
  - EG or methanol < 20 mg/dL (3.2 mmol/L for EG; 6.2 mmol/L for methanol)
  - Correction of metabolic acidosis

Barceloux EP 1999; Barceloux EP 2002

Fomepizole monotherapy

- Many case reports of patients with EG poisoning successfully treated by fomepizole monotherapy
  - Important message: only for early cases - normal renal function and no metabolic acidosis
- A case of lowest arterial pH of 7.12 on admission (Baud FJ, et al 1988)

Fomepizole monotherapy for methanol poisoning?

The role of HD when fomepizole is used

	EG	Glycolate	Methanol	Formate
Renal clearance	17 – 39 ml/min		1 ml/min	
Half-life + fomepizole	~20 h		~52 h	
Half-life + ethanol	11 – 18 h		30 – 52 h	
Half-life under dialysis	150 – 210 min	155 ± 474 min	197 – 219 min	150 ± 37 min
Half-life spontaneous		625 ± 474 min		205 ± 90 min

Due to methanol's long elimination half-life in ADH inhibition, antidote administration must be prolonged even in case of normal renal clearance
The use of fomepizole should obviate the need for HD in EG!

Mégabane B 2005; Mégabane B 2010

Revised recommendations for HD in EG and methanol poisoning

Mégabane B 2005; Mégabane B 2010

EG: Renal failure (Serum Cr >265 µmol/L or rise by >90 µmol/L
Methanol: Visual or neurological impairment
Deteriorating vital signs despite ICU care

Arterial pH < 7.1
Inability to correct metabolic acidosis despite bicarbonate infusion:
-Drop in arterial pH > 0.05 resulting in a pH outside the normal range
-Inability to maintain arterial pH > 7.3
-Decrease in bicarbonate concentration >5 mmol/L

Rate of methanol decline <10 mg/dL (3.1 mmol/L)/d
Initial serum EG or methanol ≥ 50 mg/dL (nonacidotic)?
(8.1 mmol/L for EG; 15.6 mmol/L for methanol)?

Intermittent HD vs CVVHD/HDF in methanol poisoning

- 11 intermittent HD and 13 CVVHD/HDF patients during an outbreak of methanol poisonings in Czech Republic in 2012

	Intermittent HD	CVVHD/HDF
Mean methanol elimination half-life	3.7 ± 1.4 h	8.1 ± 1.2 h
Mean formate elimination half-life	1.6 ± 0.4 h	3.6 ± 1.0 h

In methanol poisoning outbreak in resource-limited area, a minimum of 8 h of IHD or 18 h of CVVHD/HDF before discontinuation of the dialysis, if the methanol concentration or the osmolal gap cannot be measured, provided that the metabolic acidosis is corrected, and ADH is blocked.
Continued ADH inhibition treatment for at least 12-24 h after discontinuation of the dialysis

Zakharov S, et al. Kidney International 2014

Endpoint of HD

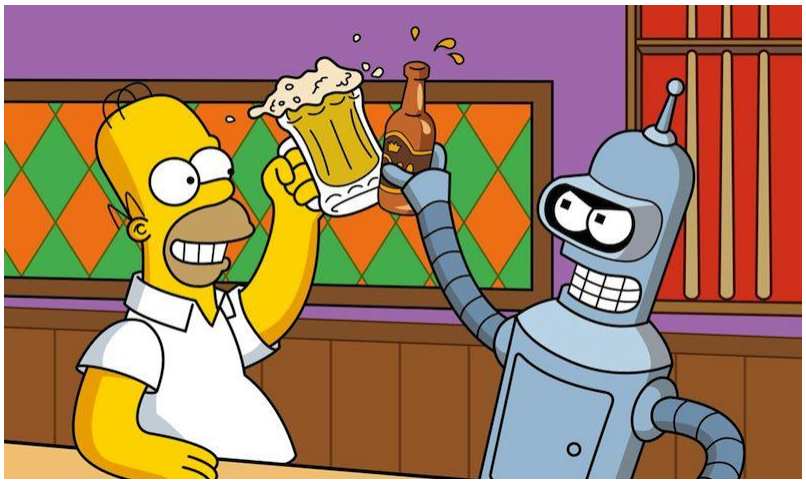
- Resolution of acid-base disturbance
- Resolution of osmolar gap (good correlation with serum methanol concentration)
- Plasma toxic alcohol concentration < 20 mg/dL
- (< 50 mg/dL if given ADH inhibition, no renal failure, no acidosis)
- 8-h duration of HD should general be sufficient (when the alcohol concentration is not known)
- NOT resolution of visual or ocular abnormalties

- Monitoring after cessation of HD:
  - Redistribution of toxic alcohols may result in rebound of serum concentration
  - Monitor serum level q2-4h for 12-36h after stopping HD

Hunderi OH 2006
Mégarbane B 2010
Barceloux EP 1999; Barceloux EP 2002

Bring home message

- Not always a clear-cut diagnosis
  - Interpretation of osmolar gap
  - Limitation in screening tests and confirmatory tests
- Predictors of severe toxicity: metabolic acidosis and end-organ damages, NOT serum EG or methanol levels
- Fomepizole may be better than ethanol
- Fomepizole may obviate the need for HD in stable patient with EG poisoning, but need close monitoring
- Definitive treatment is HD
- Choice between IHD vs CVVHD / HDF



The end

Thank you for your attention