ALCOHOL TOXIDROMES

ETHANOL:

ETHANOL CAUSES CNS DEPRESSION THAT IS SYNERGISTIC WITH OTHER CNS DEPRESSANTS AND IS FREQUENTLY CO-INGESTED, HENCE CONFOUNDING ASSESSMENT IN DELIBERATE SELF-POISONING

CARE IS SUPPORTIVE

RISK ASSESSMENT:

- Ethanol ingestion causes a rapid and dose-related CNS depression
- High amount of inter-individual variability
- Co-ingestion with other depressants ↑s risk of respiratory depression
- Seizures may occur either in the setting of INTOXICATION or WITHDRAWAL

TOXIC MECHANISM:

- The molecular sites of action are uncertain, but augmentation of GABA-A is thought to be central to its CNS effects
- Other sites may include glycine, NMDA, serotonin, adenosine and L-type Calcium channels
- DOSE-DEPENDENT cardiovascular depression
- Gluconeogenesis is impaired → HYPOGLYCAEMIA

TOXICOKINETICS:

- RAPIDLY ABSORBED and is distributed over the total body water (Vd = 0.6L/kg)
- Oxidised by ALCOHOL DEHYDROGENASE (ADH) to acetaldehyde, thence to ACETYL CoA by ALDEHYDE DEHYDROGENASE
    - Both steps involve reduction of NAD to NADH → this ↓s conversion of lactate to pyruvate and inhibits gluconeogenesis and fatty acid oxidation (leading to ↑lactate and ↓BSL respectively)
- Above 4 mmol/L → ZERO ORDER ELIMINATION KINETICS
    - A constant amount metabolised per unit time
    - In most patients, serum levels ↓ by 0.02% per hour (4mmol)

CLINICAL FEATURES:

- FEATURES ARE PROGRESSIVE WITH WORSENING INTOXICATION

- Disinhibition, lability, euphoria
- Nystagmus, ataxia, slurred speech
- Agitation, aggression, disorientation
- Nausea/vomiting
- Tachycardia, hypotension, hypothermia
- Coma, respiratory depression, loss of airway reflexes

Worsening intoxication. Dependent individuals are ambulant at higher blood alcohol levels than non-dependent.

INVESTIGATIONS:

- In all poisoned patients, 12-lead ECG, BSL and paracetamol level
- Serum ethanol levels assist risk assessment in patients with CNS depression → BUT DO NOT BE REASSURED IF LEVEL ELEVATED, AS OTHER FACTORS MAY BE AT PLAY
- Breath analysis is influenced by minute ventilation

MANAGEMENT:

- RESUSCITATION AS APPROPRIATE
- Give thiamine liberally
- Be sure to anticipate withdrawal during observation in those who are dependent
- General supportive care is often sufficient
- No role for decontamination or enhanced elimination (even though ethanol elimination is enhanced by haemodialysis)
- No antidote
- Those with mild CNS depression are managed supportively and may be discharged with clinically well, ambulant, passing urine, eating and drinking

<u>ETHYLENE GLYCOL:</u>

A TOXIC ALCOHOL, IT IS USUALLY LETHAL IN DELIBERATE INGESTION WITHOUT TIMELY INTERVENTION

SOURCES:

- Radiator coolants in concentrations of 20-98%
- De-icing solutions
- Solvents
- Brake fluids

RISK ASSESSMENT:

- Ingestion of ≥1mL/kg is potentially lethal, but unintentional ingestion of less than a mouthful is benign
- Co-ingestion of ethanol confounds assessment as it can delay toxicity
- Dermal and inhalation exposure does not lead to intoxication

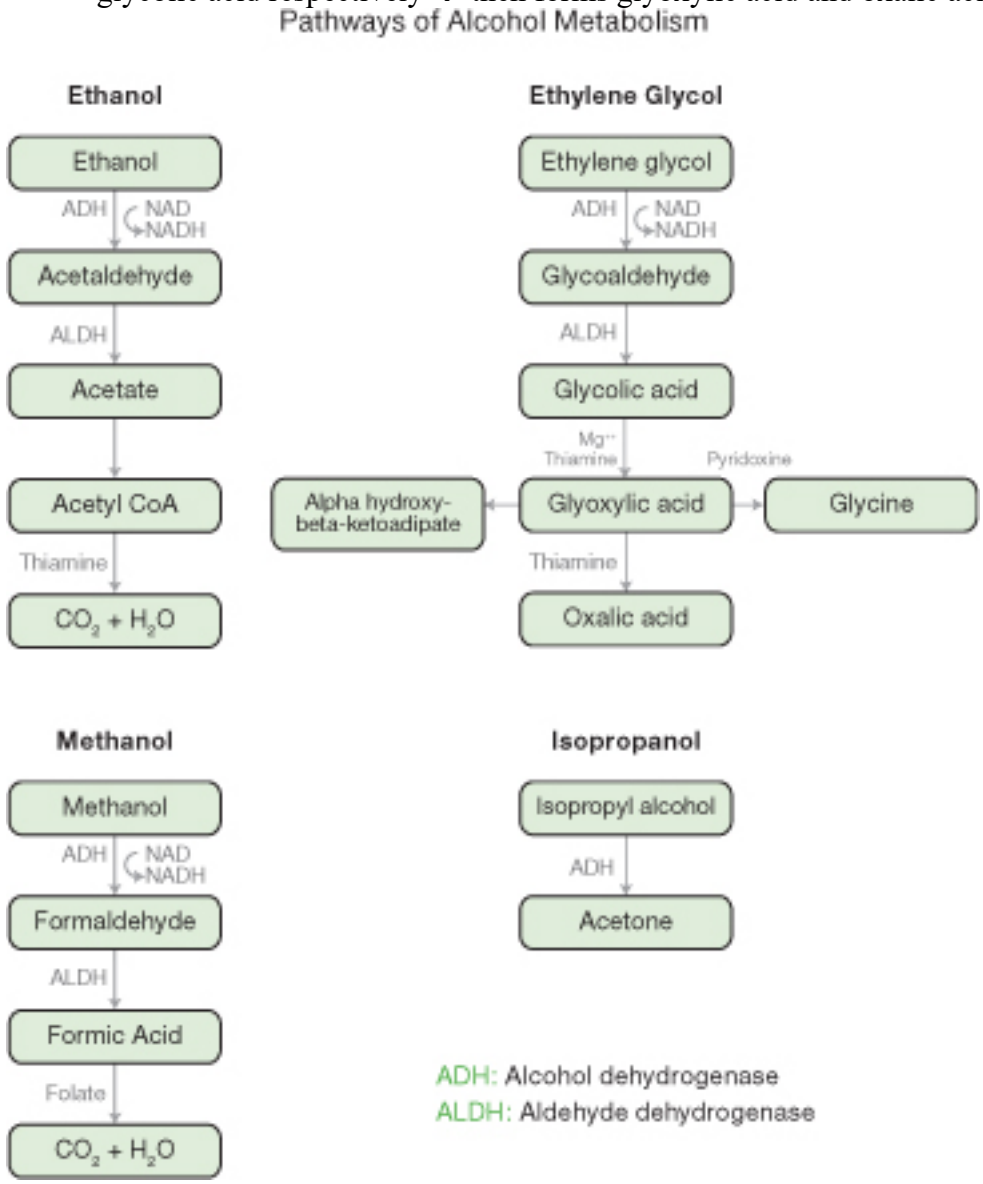
TOXIC MECHANISM:

- Causes CNS effects similar to those of ethanol
- However, the more important toxic effects are due to METABOLITES
- A SEVERE ANION-GAP ACIDOSIS develops due to accumulation of GLYCOLIC ACID AND LACTATE
- Also, CALCIUM OXALATE CRYSTALS form in tissues (renal tubules, myocardium, muscles and brain)
    - Hypocalcaemia
    - Acute oliguric renal failure (both glycolic acid and calcium oxalate are nephrotoxic)

TOXICOKINETICS:

- Rapidly absorbed, with peak concentrations reached in 1-4 hours

- Distributed across TBW with rapid CNS penetration
- Metabolised by ADH and aldehyde dehydrogenase to glycoaldehyde and glycolic acid respectively → then forms glyoxylic acid and oxalic acid



- In the absence of ADH inhibition (ethanol or fomepizole), elimination half life is 3 hours
    - Ethanol serum concentrations of 11-22mmol/L completely inhibits ADH hence PREVENTING METABOLISM OF ETHYLENE GLYCOL TO GLYCOALDEHYDE → hence half life increases to 17 hours as it has to be eliminated exclusively by the kidney

CLINICAL FEATURES:

- Three aspects of note in toxic → CNS, cardiopulmonary, renal
- RAPID COURSE:
    - First 1-2 hours similar to ethanol → euphoria, nystagmus, N+V
    - Progressively severe over next 4-12 hours:
        - Dyspnoea, ↑RR, ↑HR, ↑BP, ↓LOC → SHOCK, COMA, SEIZURES, DEATH
    - Flank pain and oliguria → acute renal failure

- Late cranial neuropathies (II, V, VII, VIII, IX, X, XII) → up to 5-20 days later

INVESTIGATIONS:

- All tox patients get ECG, BSL and paracetamol level
- EUC (including chloride), serum lactate, serum osmolality, ABG:
  - Elevated osmolar gap, anion gap acidosis and ↑lactate are surrogate markers of intoxication
  - AG acidosis, with ↑lactate, ↓Ca and ↑creatinine is PATHOGNOMONIC of EG intoxication
- Serum ethanol → tests for co-ingestion and for titration of therapy
- Serum EG → not readily available
- Urine microscopy → calcium oxalate crystals → absence does not exclude intoxication

MANAGEMENT:

- Basic resuscitation measures are crucial
- If you intubate, it is crucial to remember that EG patients are profoundly acidaemic and most have attempted to compensate by respiratory mechanisms
  - INTUBATION WITHOUT MAINTAINING HYPERVENTILATION CAN BE FATAL DUE TO ACUTE DECOMPENSATION
  - Maintain hyperventilation and consider bolus IV bicarbonate (1-2mmol/kg)
- Detect and correct ↓Ca (only if refractory seizures or ↑QT), ↓Mg, ↑K
- No role for decontamination
- ENHANCED ELIMINATION:
  - HAEMODIALYSIS IS DEFINITIVE (use lactate-free dialysate with added HCO3)
  - INDICATIONS FOR DIALYSIS:
    - History of large EG ingestion with osmolar gap >10
    - Acidaemia with pH<7.25
    - Acute renal failure
    - EG level >8mmmol/L
  - END-POINTS:
    - Correction of acidosis
    - EG level <3.2mmol/L
    - Osmolar gap <10
- ANTIDOTES:
  - Ethanol and FOMEPIZOLE (ADH INHIBITOR, not available in Australia) → TEMPORISING MEASURES PENDING DIALYSIS
  - ETHANOL:
    - ADH has much higher affinity (up to 20x) for ethanol than for EG (or for methanol) and thus inhibits conversion to toxic metabolites
    - Aim to maintain levels of 100-150mg/dl or 22-44 mmol/L
    - IV administration → loading dose of 8mL/kg of 10% and maintenance infusion of 1-2mL/kg/hour (variable between individuals) → can also use oral or NG route. IV route can cause phlebitis and ↓BSL (esp in kids)

    - FOMEPIZOLE:
        - Specific potent ADH inhibitor, but not available in Australia→ toxic alcohols are excreted unchanged in the urine
        - Induces its own metabolism when administered for > 48 hours and is dialyzable
        - Loading dose of 15mg/kg over 30mins and 10mg/kg q12h for 48hours (if dialysis being undertaken → give every four hours)
        - Superiority over ethanol is not confirmed, but ease of administration, improved adverse effect profile and more predictable pharmacokinetics with decreased need for dialysis are all potential positives
- DISPOSITION:
    - Children who remain well after suspected ingestion and have a normal venous bicarbonate at four or more hours post ingestion may be discharged
    - All symptomatic patients and those with deliberate ingestion are assumed to have potentially lethal EG intoxication
    - Dialysis may be required for WEEKS, but renal function normally returns to normal
    - Patients who survive severe intoxication are followed up to exclude development of cranial neuropathies

<u>METHANOL:</u>

TOXIC ALCOHOL, USUALLY LETHAL IN DELIBERATE INGESTION WITHOUT APPROPRIATE INTERVENTION

SOURCES:
- Chemical applications in industry and science
- Solvent in thinners, varnishes, paints and enamels
- Model aeroplane fuel
- Fuel additive
- Dyes and stains
- Wood alcohol/spirits

RISK ASSESSMENT:
- Ingestion of > 0.5mL/kg is potentially lethal (0.25mL/kg in kids)
- Ingestion of less than a mouthful is benign

TOXIC MECHANISM:
- Production and accumulation of FORMIC ACID produces a SEVERE ANION GAP ACIDOSIS and DIRECT CELLULAR TOXICITY due to inhibition of CYTOCHROME OXIDASE → lactate ↑
- Retinal injury and oedema → BLINDNESS
- CNS → SUBCORTICAL WHITE MATTER HAEMORRHAGE and PUTAMENAL OEDEMA are classic

TOXICOKINETICS:
- Methanol is rapidly absorbed → peak levels in 30-60 minutes
- Rapidly distributed across TBW

- Metabolised by ADH to formaldehyde and thence by ALDH to FORMIC ACID
- Elimination half life is 24 hours → ↑s to 43 hours with ADH inhibition as methanol is exclusively excreted by the kidney

CLINICAL FEATURES:
- Mild CNS depression similar to ethanol intoxication within one hour
- LATENT PERIOD OF 12-24 HOURS:
    - Headache, vertigo, SOB, blurred vision
    - More severe symptoms → ↑RR, drowsiness and blindness
    - Progressive obtundation → coma and seizures (cerebral oedema)
        - Papilloedema is characteristic of demyelination and up to 1/3 patients suffer irreversible visual complications
- Those who recover from serious CNS toxicity frequently display extrapyramidal movement disorders

INVESTIGATIONS:
- All tox patients get ECG, BSL and paracetamol level
- EUC, lactate, ABG, osmolality
    - Anion gap acidosis, ↑lactate and elevated osmolar gap are surrogate markers of intoxication
- Serum ethanol → co-ingestion and titration of treatment
- Serum methanol → not readily available
- Radiology → CT brain → characteristic injury to basal ganglia in those with permanent neurological injury

MANAGEMENT:
- Attention to basic resuscitation principles are paramount
- Similar to EG intoxication → if you intubate, ensure that HYPERVENTILATION IS MAINTAINED, otherwise acute decompensation can occur (consider HCO3 1-2mmol/kg bolus pending dialysis)
- SYSTEMIC ACIDOSIS ENHANCES FORMIC ACID INHIBITION OF CYTOCHROME OXIDASE → hence if pH <7.30 → 50mmol bicarb until this level is reached
- FOLINIC ACID:
    - Cofactor treatment, given at 2mg/kg q6h until poisoning definitively treated
    - Active form of folic acid (more routinely given post-high dose methotrexate in oncological practice)
- No role for GIT decontamination
- ENHANCED ELIMINATION:
    - Haemodialysis is the definitive management of methanol intoxication as it removes methanol and formic acid and corrects the acidosis
        - Lactate free dialysate with added bicarbonate
    - INDICATIONS FOR DIALYSIS:
        - pH<7.30
        - Visual symptoms
        - Renal failure
        - Deterioation of vital signs or electrolyte status despite supportive care

        - Methanol level > 16mmol/L
    - END-POINTS:
        - Correction of acidosis
        - Osmolar gap<10
        - Methanol level <6mmol/L
- ANTIDOTES:
    - Ethanol and fomepizole → TEMPORISING MEASURES PENDING DIALYSIS

<u>ISOPROPYL ALCOHOL (ISOPROPANOL):</u>

PRODUCES A CNS INTOXICATION SYNDROME IDENTICAL TO THAT OF ETHANOL, BUT IT IS MORE POTENT

CAUSES MARKED GIT IRRITATION AND KETOSIS WITHOUT ACIDOSIS

SOURCES:
- 50-70% concentration found in disinfectants, solvents, window cleaners and perfumes

RISK ASSESSMENT:
- Causes dose-related CNS-depression
- As little as 1mL/kg of 70% can cause inebriation, 4mL/kg can lead to coma and respiratory depression → risk ↑d by coingestion of other CNS depressants
- Significant toxicity can be achieved in kids with dermal absorption (rubbing alcohol as an antipyretic measure)

TOXIC MECHANISM:
- Molecular sites of action are uncertain but augmentation of GABA-A thought to be central
- Production of acetone and ketonaemia may contribute to CNS depression
- Severe AG acidosis IS NOT A FEATURE
- Isopropanol itself is a GI IRRITANT

TOXICOKINETICS:
- **RAPIDLY AND WELL ABSORBED FOLLOWING INGESTION, DERMAL CONTACT OR INHALATION**
- Distributes across TBW
- 40% of absorbed dose excreted unchanged by lungs and kidneys, the rest being metabolised by hepatic ADH to ACETONE

CLINICAL FEATURES:
- Intoxication syndrome IDENTICAL TO ETHANOL but more potent
- Duration of inebriation longer and may have more marked GI irritation and ketosis than with ethanol

SUPPORTIVE CARE CENTRAL TO MANAGEMENT → only consider dialysis if there is profound coma and hypotension refractory to fluid resuscitation

OTHER TOXIC ALCOHOLS:

BENZYL ALCOHOL, DIETHYLENE GLYCOL, EGBE, EGME, PROPYLENE GLYCOL, TRIETHYLENE GLYCOL → found in a rang e of automotive products, solvents and pharmaceuticals → deliberate self-poisoning is potentially lethal

TOXIC MECHANISM:

- CNS effects similar to ethanol, with more significant toxicity be a function of toxic metabolites (including lactate)
- The cardiovascular and CNS effects of propylene glycol appear to be a direct toxic action

TOXICOKINETICS:

- Rapidly absorbed following ingestion and distributed across TBW
- Metabolised sequentially by ADH and ALDH to various alkoxyacetic acid products

CLINICAL FEATURES:

- Initial features similar to ethanol → progressively severe features over ensuing hours with evolving lactic acidosis
- Severe effects include coma, seizures, refractory shock and renal failure
- Onset of toxicity may be delayed with glycol ethers
- Over rapid IV administration of agents containing propylene glycol is associated with sudden CV collapse

MANAGEMENT:

- Resuscitation → maintain hyperventilation if intubated
- Haemodialysis if:
    - Serum pH <7.3
    - HCO3 <20
    - Osmolar gap >10
    - Worsening lactic acidosis despite supportive care
    - Deteriorating vital signs despite supportive care
- Consider IV ethanol or fomepizole in treatment of glycol ether intoxication prior to dialysis