Salicylate

Overview

Potentially life threatening poisoning characterised by acid-base & electrolyte disturbances and decreasing LOC. E.g. aspirin, PeptoBismol, methylsalicylate (oil of wintergreen, 5g ≡ 7.5g aspirin, or 1ml ≡ 1400mg aspirin), choline salicylate (in Bonjela, 1mg=0.75mg aspirin)

Toxic mechanisms

Respiratory alkalosis: early directly stimulation of the respiratory centre → ↑RR. This may be transient or absent in young children.
Metabolic acidosis with ↑AG - uncoupling of oxidative phosphorylation & inhibition of TCA (→ ↑VO_2, ↑CO_2, ↑heat production, ↑glucose utilisation, ↑lactic acid) & Urea (↑ammonia) Cycles. Also COX inhib → ↓PG syn. Acidosis worsened by organic acid metabolites, starvation & ketosis.
Glucose metabolism: Hypoglycaemia (intracellular > extracellular) may occur due to ↑peripheral glucose demand, ↑rate of tissue glycolysis, ↓rate of glucose synthesis. However hyperglycaemia may occur due to increased glycogenolysis.
Other effects: K^+ depletion occurs because of increased renal excretion as well as intracellular shift. Hypokalaemia prevents the production of alkaline urine.
Salicylates competitively inhibit Vit K dependent synthesis of factors II, VII, IX & X → ↑INR.
Salicylates may cause a mild dose dependent hepatitis & >6% salicylate sol can → skin/GI burns.

Toxicokinetics

Aspirin is a weak acid (pKa = 3.5), as pH falls a larger proportion is un-ionised and lipid soluble.
Absorption - rapidly absorbed (peak ~1hr or 4-6 if enteric coated) and hydrolysed to salicylic acid and acetic acid. Better absorbed from stomach (if not enteric coated) than ileum as pH lower unless enteric coated. Can cause pylorospasm in OD. In overdose tablet dissolution may be extremely slow and pharmacobezoars may form.
Distribution - Albumin bound (50-80% - falls with ↑blood conc). V_d 0.1-0.3L/kg. In OD > 1-2g protein binding may be saturated, also ↑ionisation with ↓pH, both → ↑↑V_d & ↑CNS penetration.
Metabolism & Elimination - ~5-10% is excreted unchanged as salicylic acid. Else hepatic met by:

- Major, but saturatable pathways (~90%): oxidation (microsomal) or glycine conjugation → salicyluric acid (majority) or glucuronide conjugation → salicyl phenoloic glucuronide.
- Minor, non-saturatable pathways (~5%): glucuronide conjugation → salicyl acyl glucuronides, oxidation to gentisic acid, 2,3-di- & 2,3,5-tri-hydroxybenzoic acid.

Therapeutic $T_{\frac{1}{2}}$=2-4.5hr, but in OD $T_{\frac{1}{2}}$~18-36hr. Done nomogram not useful. In OD renal elim more important (as much as 65%) & may be enhanced by alkaline urine.
Salicylate excretion depends on - Blood and urine pH, [K+], pre-existing liver/renal failure, dose.

Clinical features

Acute intoxication:
Progressive onset over up to 12hrs (24hrs if enteric coated) then rapid deterioration possible.
Gastro: N & V, Gastritis
CNS effects: N & V, tinnitus, confusion, hyperventilation, hallucinations, seizures, coma, cerebral oedema **(NB Serious toxicity can still occur even as salicylate level is falling, as correction of the pH causes CNS cell ion-trapping.)**
Metabolic: Hyperventilation - Acid-base disturbance (respiratory alkalosis, metabolic acidosis), dehydration (chronic > acute OD), electrolyte disturbances (hypoNa, hyperNa, HypoK, HypoCa), hypo/hyperglycaemia, fever (↑metabolic activity), diaphoresis
Other: Haem (↑PT, ↓plt aggreg – aspirin), mild ↑transaminases, rare non-cardio pulm oedema.

Chronic intoxication:
Subtle onset over days with ↓GI symptoms & ↑non-specific neuro ones. More common in elderly.
Features: confusion, delirium, dehydration, ↑T, metabolic acidosis, cerebral or pulm oedema.

Investigations

Deliberate OD screening tests: ECG, BSL, paracetamol level.
Specific: Salicylate level (NR 1.1-2.2mmol/L. Poor clinical correlation. Serial levels may show ongoing absorption or failure of Rx), ABG, urinary pH, (other FBC, UEC, CMP, LFT, Coags, AXR)

Risk Assessment

- Dose ingested (Max therapeutic dose ~80-100mg/kg/d [or 4g], acute OD of <150mg/kg trivial, 150-300mg/kg mild-mod, 300-500mg/kg severe, >500mg/kg life- threatening)
- pH: Stage I: serum pH_s>7.4, urine pH_u>6, Stage II: pH_s>7.4, pH_u<6, Stage III: pH_s<7.4, pH_u<6
- Salicylate level, while not good correlation with clinical severity, is used to chart progress and very high levels to instigate haemodialysis.
- Chronic OD has greater risk of adverse outcome. Chronic toxicity can develop from doses of 30-100 mg/kg/day. Patients with cirrhosis, low protein states or renal impairment develop toxicity with lower doses.
- Small volumes of methylsalicylate containing products have potential for severe toxicity.

Management

Resuscitation & Supportive.

- If intubated, **must** maintain a compensatory respiratory alkalosis else rapid deterioration.
- Aggressive rehydration and maintain urine output of 1.5-2ml/kg/h
- Control seizures with BDZ, glucose. Give glucose (even if BSL normal) also if ↓GCS.
- Correct any hypoK^+ (if P/U), and ensure [K^+] remains normal to allow for alkalinisation.
- Vitamin K if ↑INR or ↑PT
- Maintain normothermia, consider PPI

Decontamination - Activated charcoal PO if presenting <8hr & ingested more than 150 mg/kg. If >300mg/kg ingested give by NG, after securing airway if necessary. Repeat dose in both cases after 4hr if salicylate level rising. WBI may be considered in large enteric coated salicylate ingestions with bezoar formation, little evidence more effective.
Elimination enhancement
Urine alkalinisation (see IV **sodium bicarbonate**) to pH_u>7.5 if symptomatic (not ACS/APO/RF). Haemodialysis is rarely needed, but is preferred over haemoperfusion as it also corrects acidosis and electrolyte imbalances. Indications:

- Pre-existing cardiac or renal failure
- Failure of decontamination & urinary alkalinisation to keep level below 4.4mmol/L
- Clinically serious toxicity (altered mental state, acidaemia, renal failure, severe electrolyte imbalance, pulmonary oedema)
- Salicylate >7.2mmol/L (100mg/dL) in acute ingestions or >4.4mmol/L (60mg/dL) in chronic or children/elderly.

Disposition

Therapy ceased when salicylate level and ABG in NR.
ICU if acute ingestion >300 mg/kg or significantly symptomatic.

Notes

Long term sequelae (neuropsychiatric) are a significant risk in severe poisonings due to the potential for damage from acidosis, hypoglycaemia and hypoxia. Risk factors: Old age, seizures, coma on admission, low pH, low Po_2, low K, chronic toxicity.