Pharmacology week 16 - NSAIDs

Basic pharmacology of NSAIDs

Chemistry
- weak organic acids (except nabumetrone – ketone prodrug)
- some racemic mixtures (ibuprofen)
- single enantiomer (naproxen)
- no chiral centre (diclofenac)

PK
- good oral absorption unaffected by food
- highly metabolised (phase I – CYP, phase II – glucuronidation)
- most high PB
- renally excreted (variable biliary excretion)

PD
- mech: inhibits PG synthesis, production TxA2 via inhibition COX, decr sensitivity vessels to bradykinin and histamine, decr lymphokine production
- clinical effects: analgesia, antipyretic, anti-inflammatory, inhibit plt aggregation (aspirin irreversibly)
- chronic use decr. inc colon cancer

Aspirin
Class – acetylsalicylic acid, simple weak organic acid, from willow bark, active ingredient = salicylic acid. Non-opioid analgesic, NSAID (salicylic acid pKa 3.0, aspirin pKa 3.5)

PD
1. binds irreversibly COX – at low dose decreases plt TxA2, higher dose decreases tissue prostacyclin (antiplt – irreversible, duration = life of plt ~8/7)
2. inhibits kallikrein system (via inhibition kallikrein mediated PG)
3. analgesic i) decr inflamm mediators ii) ?subcortical site
4. antipyretic i) vasodilatation ii) decr IL-1 by macrophages: decr hypothalamic response
A – absorbed rapidly in stomach (acid pH) and duodenum, peak plasma level 2hrs
D - 1. Absorbed as ASA, hydrolyzed to acetic acid and salicylate (blood and tissue esterase)
2. binds albumin (saturable) Vd 10L, PB 80%
M - 1. Mostly conjugated with glucuronide and glycine by liver.
2. Analgesic/antipyretic dose 600-1200mg / d. First order kinetics - half life 3 - 5 hours.
3. Anti-inflam dose > 4g/d - zero order kinetics - half life >15 hours - saturation hepatic enzymes
E – renal excretion, incr by alkalinizing urine
Ind – mild-mod analgesia, anti-inflam, anti-pyretic, plt inhibition, recurrent miscarriages, HEELP, prophylaxis MI/CVA
Cl – haemophilia, ?Reyes syndrome, pregnancy
Prec – GI ulceration, bronchospasm
Int – incr risk salicylate intox with acetazolamide, EtOH incr risk GI bleeding, displaces from PB – phenytoin, tolbutamide, methotrexate, decr renal tubular secretion penicillin
SEs – GI (GI, ulceration); salicylism (reversible) (tinnitus, vertigo, decr hearing), low dose decr secretion ural acid, high dose incr secretion – uricosuric, decr GFR via decr PGI 2, confusion, fever, dehydration (shift arachidonic acid from prostaglandin to leukotriene pathway – asthma)
Tox - 1. Respiratory alkalosis - peripheral - increased CO2 produced by skeletal muscle stimulates medullary respiratory centre causes increased RR and VT
2. Renal compensation - for resp alkalosis
3. Further metabolic acidosis:
   i) salicylic acid dissociation giving increased H+
   ii) deranged CHO metabolism leads to lactic, pyruvic, acetoacetic acid accumulation
   iii) decr vasomotor function causes decreased renal function and increased PO4/SO4 levels.
   iv) 150mg/kg potentially toxic, >500mg/kg very toxic

Ix: ECG, ABG, panadol level, salicylate level (1.1-2.2 mmol/L therapeutic) NB tablet bezoar
Mx: charcoal up to 8hrs, urinary alkalinisation, (Ion trapping – alkalinize urine – salicylate in renal tubules ionized – can’t be reabsorbed), haemodialysis is high levels or levels rising (even though high PB, PB is saturated), fluids, supportive, ?ventilation

Classes of NSAIDs
Salicylates (ASA)
Nonacetylated salicylates: COX-2 inhibitors (celecoxib)
Nonselective cox inhibitors: mfenamic acid, diclofenac, indomethacin, sulindac, peroxicam, ibuprofen, naproxen
Cox-2 inhibitors
- aim to decrease GI sx by selective cox2 inhibition
- preferable in asthma and bleeding tendencies
- higher incidence CVS thrombotic events
- Celecoxib a sulphonamide (allergy), interacts with warfarin

Diclofenac
- 20% have GI effects; may impair GFR, may incr LFTs

Ibuprofen
- 2400mg/d equal anti-inflam effect to aspirin, at lower doses only analgesic effect
- less decrease in UO and less fluid retention
- closes PDA in preterm infants equal to indomethacin
- GI effects less than aspirin
- CI in nasal polyps, angioedema, bronchospasm with aspirin
- can cause ARF, interstitial nephritis, nephritic syndrome (like all NSAIDs)

Indomethacin
- potent non selective COX inhibitor
- may inhibit phospholipase A/C, reduce neutrophil migration and decrease T and B cell prolif
- for rheumatic conditions, gout, Ank spond, PDA
- GI effects, headache, haematological reactions, hyperkalaemia, renal papillary necrosis

Piroxicam
- at high concs inhibits PMN migration, decr O2 radical production, inhibit lymphocyte fxn
- long t1/2 – once daily dosing
- GI sx, tinnitus, headache, rash (much higher risk GI ulcer)

Tenoxicam
- similar to pirocam, long t1/2

Paracetamol
Class – analgesic, antipyretic; active metabolite of phenacetin
PD – weak cox 1,2 inhibitor - ?cox3. No uricosuric antagonism (probenicid)
A – rapid complete absorption GI, peak plasma 30-60mins
D – Vd 1L/kg, 20-50% PB
M – therapeutic dose mainly hepatic, t1/2 2-3hrs, >95% conjugation principally with glucuronide, also with sulphate (t1/2 >6hrs in overdose), minor metabolite = N-acetyl-P-benzoquinone.
E – metabolites renally excreted
Ind – analgesia, fever
CI – hypersensitivity, liver disease, infants <1/12
Int - nil
SEs/tox – mild ↑ LFTs, haemolytic anaemia, maemoglobinaemia (rare), rash (rare)
Tox – hepatotoxicity, renal toxicity (ATN, ARF) – toxic dose 200-250mg/kg, initial N/V/A/AP; 2/7 later incr transaminases, LDH, INR; encephalopathy; centrilobular necrosis
Use nomogram 4hrs post ingestion. Toxicity - N-acetyl-P-benzoquinone (NAPQI), usually inactivated by reduced glutathione (GSH). In toxic doses saturation of normal conjugation pathway, shunted into alternative NAPQI pathway. Treatment - N-acetylcysteine. Exac by alcoholism, starvation, CYP inducers.

N-acetylcysteine
- pref. within 8 hrs, IV loading dose, then IVI 17 hrs
- SEs: mild anaphylactoid reactions (slow infusion, antihistamines and fluid)
- sulphhydril donor
- 4 possible mechanisms:
  1. increased glutathione availability
  2. direct binding to NAPQI
  3. provision of inorganic sulphate
  4. reduction of NAPQI back to paracetamol
150mg/kg in 200ml 5% dext 15min
50mg/kg in 500ml 5% dext 4 hrs
100mg/kg in 1000ml 5% dext 16 hrs

Colchicine
Class – alkaloid anti-inflammatory agent selective for gout
PD -
  1. Relieves pain of gouty arthritis without affecting metabolism or excretion of urates
  2. Binds to intracellular protein TUBULIN, prevents it from polymerizing into microtubules
  3. Inhibition of leukocyte migration to inflamed area
  4. Inhibits formation of leukotriene B4
A – po rapid, peak plasma level in 2hrs
D – predom to GI tract, also kidney, liver, spleen (heart, skeletal muscles, brain relatively spared)
M – extensive hepatic deacetylation
E – predom in faeces, urine 10-20%, t1/2 90 mins
Ind – prevent/abort attacks gout during initiation allopurinol or uricosuric agent
Prec – elderly, debilitated, GI ulcer
SEs – N/V/D/AP/haemorrhagic gastroenteritis, leukopenia then leucocytosis, agranulocytosis, aplastic anaemia,
myopathy, metabolic acidosis
Int – incr risk toxicity with alcohol, anticoagulants
Tox – chronic: hair loss, bone marrow suppression, peripheral neuritis, myopathy; acute: burning throat pain, bloody
diarrhoea, shock, coagulopathy, haematuria, ARF, ascending paralysis of CNS.0.5-0.8mg/kg toxic, >0.8mg/kg severe
poisoning. See GI Sx for 2hrs – 2 days than multi-organ toxicity
Treatment supportive, charcoal, large volumes fluid, monitor fluid/electrolyte/acid-base status

Allopurinol
Class: Antihyperuricaemic
PD: inhibits Xanthine oxidase
PK: Oral availability: >0.8 Vd: 42L/70kg
P.B: <0.05; t1/2: 0.5-2hr
fu: 0.1-0.3, 0.8 oxypurinol Cl: ≈ 90L/hr/70kg oxypurinol
Metabolism: hepatic by hydroxylation (xanthine oxidase) to oxipurinol
E: renal
Ind: Reduction of uric acid/urate production (chronic gout, skin tophi, nephrolithiasis);
2° hyperuricaemia (malignancies; calcium oxalate renal stones associated with hyperuricosuria
Prec: Acute gout, Pregnancy, Lactation
SEs: rash, drowsy, fever, N/V/AP, gastritis, dyspepsia, ↑ LFTs, jaundice, peripheral neuropathy, SJS, aplastic anaemia
Int: Inhibits metabolism of azathioprine, Pan CYP inhibitor↑ toxicity of warfarin, theophylline; Thiazides enhance
toxicity in renal tubules; Probenecid/salicylates - may accelerate excretion of oxypurinol
OD – GI sx; → hydration to maintain diuresis. Consider dialysis

Uricosuric agents (probenecid, sulfinpyrazone)
PK – completely resorbed from renal tubules
PD – affects active secretion and reabsorption pathways for acids in kidney
- decr net reabsorption uric acid in PCT; blocks active secretion into tubules
Ind – gout 2-3/52 post attack, prolong duration penicillin
SEs – GI, allergic dermatitis, nephrotic syndrome, aplastic anaemia

DMARDs
Methotrexate
- MOA: inhibition AICAR transformase and dihydrofolate reductase
- PK: 70% oral absorption, stays intracellular longterm, t1/2 6-9hrs, 70% urinary excretion
- SEs: nausea, mucosal ulcers, dose related hepatotoxicity
Gold
- MOA: alters morphology and function of macrophages
- PK: t1/2 1 yr, 2/3 renally excreted
Sulfasalazined
- PK: low oral absorption, t1/2 6-17 hrs
- SEs: N/V/HA, neutropenia, methaemoglobinemia
Chloroquine
- PK: deaminated in liver, slow acting: 3-6 months till effect, t1/2 45 days
Azathioprine
- MOA: suppress inosinic acid function
- PK: 0.3% slow metabolisers (incr SEs); SEs: GI, bone marrow suppression
Cyclosporine
- MOA: regulation gene transcription
- PK: erratic absorption, incr by grapefruit, metabolised CYP3A4 – lots of interactions
Cyclophosphamide
- MOA: cross links DNA to prevent cell replication
Chlorambucil (prodrug)
- MOA: cross links DNA