PAIN

Dr S Mathijs

PAIN PATHWAY

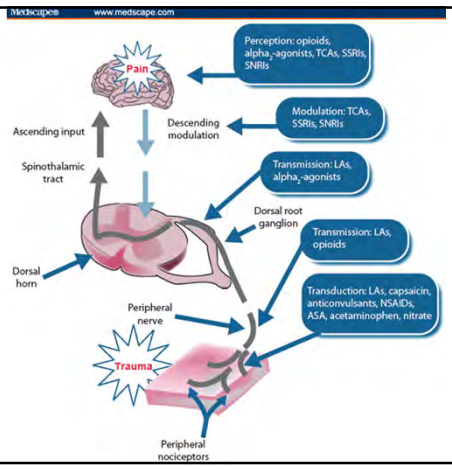
- Nociception is registration of painful stimuli, associated with stimulation of pain receptors (nociceptors)
- Action potential transmitted by thin Aδ fibers and non myelinated C fibers to dorsal horn and spinal cord
- Signal transmitted to thalamus and brain stem
- Bradykinin, prostaglandins, neurotransmitters, ions, metabolites from damaged tissues implicated
- Glutamate, ATP, substance P and calcitonin gene-related peptide (CGRP)–fast neurotransmitters of primary nociceptor fibers
- Opioid peptides, endocannabinoids, 5HT, NA involved in modulating pathway

PAIN

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Perception of pain is an outcome of the neural activity of pain transduction, transmission, and modulation and is influenced by behavioural and emotional factors
- Acute or chronic

PAIN SOURCE

Visceral (nociceptive)	• Originates in smooth muscle • Difficult to localize • Responds to opioids
Somatic (nociceptive)	• Originates in skeletal muscle, ligaments, joints • Localized and constant • Responds to NSAIDs
Neuropathic pain	• Peripheral or central nerve injury, not stimulated • Burning, shooting, tingling pain • Responds to adjuvant Rx



CATEGORIES OF ANALGESIC DRUGS

- Opioid analgesics
- Non opioid analgesics
- Adjuvant analgesics

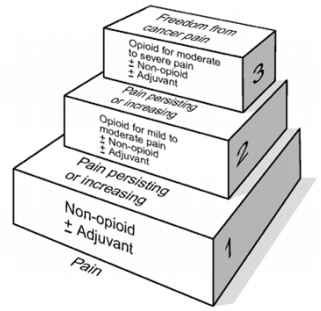
CHOICE OF THERAPY

- Severity
- Source
- Acute vs chronic
- Pt's age
- Comorbidities

ROUTES OF ANALGESICS

- Oral
- Rectal
- Parental: IMI, IVI, sc
- PCA
- Regional nerve blocks

SEVERITY OF PAIN



SITES OF ACTION OF ANALGESICS

- At site of injury: NSAIDs
- Blocking peripheral nerves: local anaesthetics
- Closing "gates" in dorsal horn and thalamus: opioids and TCA
- Change central appreciation of pain: opioids

ACUTE VS CHRONIC PAIN

- Opioids and NSAIDs effective in acute pain
- Less effective if administered chronically
- Adverse effects can worsen with chronic therapy
- Adjuvants not effective for acute pain

NEUROPATHIC PAIN

- Abnormal physiology of peripheral or central nervous system and may be unrelated to ongoing tissue damage or inflammation
- Serves no useful purpose
- Sustained and chronic

EXAMPLES OF NEUROPATHIC PAIN

- Diabetic peripheral neuropathy
- HIV sensory neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
- Phantom limb pain
- Poststroke pain
- Multiple sclerosis pain
- Infiltration of tumour

1ST LINE TREATMENT OPTIONS

- Gabapentin
- 5% lidocaine patch
- Opioid analgesics
- Tramadol hydrochloride
- TCA

ADJUVANT ANALGESICS

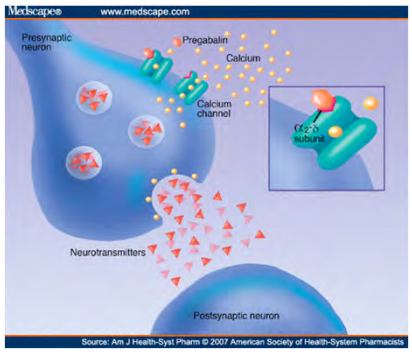
- Defined as drugs with other indications that may be analgesic in specific circumstances
- Numerous drugs in diverse classes
- Combinations often needed
- Often added if opioids/NSAIDs have failed
- Lower doses may be effective than those required for their primary indication
- Chronic use

GABAPENTIN

- Antiepileptic
- GABA analogue
- MOA: ? Calcium channels in CNS
- Well tolerated
- SE: drowsiness

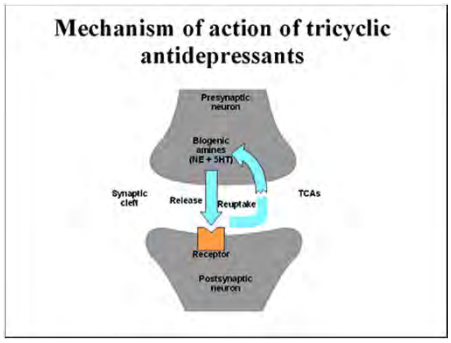
ADJUVANT THERAPY

- Anticonvulsants
- Antidepressants
- Local anaesthetics
- Corticosteroids
- Other



PREGABALIN

- Postherpetic neuralgia
- Diabetic polyneuropathy
- Start low, increase gradually
- Additive CNS effects with other depressants
- SE: dizziness, somnolence, blurry vision



5% LIGNOCAINE PATCH

- Peripheral acting topical analgesic
- MOA: block sodium channels
- Minimal systemic absorption
- 4 patches in 18 hours

SECOND LINE DRUGS

- Anticonvulsants
- Antidepressants
- Corticosteroids
- Topical analgesics

TCA

- Amitriptiline
- MOA: inhibit reuptake of noradrenaline and serotonin
- SE: anticholinergic, CVS
- Drug interactions with drugs metabolized by CYP2D6

ANTICONVULSANTS

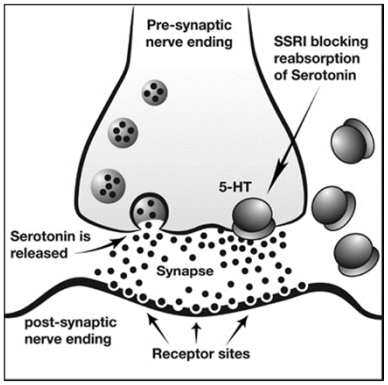
- Lamotrigine: sodium and calcium channels, Steven Johnson's syndrome
- Carbamazepine: sodium channels, trigeminal neuralgia
- Oxcarbamazepine

ANTIDEPRESSANTS

- SSRI: paroxetine ,citalopram
- SSRI and SNRI: venlafaxine, bupropion, duloxetine

NMDA RECEPTOR ANTAGONISTS

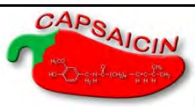
- N-methyl-D-aspartate receptor involved in neuropathic pain
- **Ketamine**
- **Dextromethorphan**
- **Methadone**
- Reserved for refractory cases



MUSCLE RELAXANTS

- BZD
- Baclofen: trigeminal neuralgia

TOPICAL ANALGESICS



- **Capsaicin cream**: depletes substance P, desensitizes nerve fibres
- Skin irritation limits use

- **EMLA:** lignocaine and prilocaine
- **Menthol, methylsalicylate**: creams, ointments, gels, lotions
- May be effective for arthritic pain
- NB skin injury

OPIOIDS

OPIOIDS

- Opium derived from poppy seed
- Opium mixture of alkaloids- morphine, codeine, papaverine
- Osler: “God’s own medicine”
- Odysseus: “banish grief or trouble from mind”

OPIOID RECEPTORS

- **μ,δ, κ, σ receptors**
- Stereospecific receptors in neuronal membranes in PAG, limbic system, thalamus, hypothalamus, medulla oblongata, substantia gelatinosa
- Encephalins are inhibitor transmitter substances

OPIOID THERAPY

- 1st line therapy:

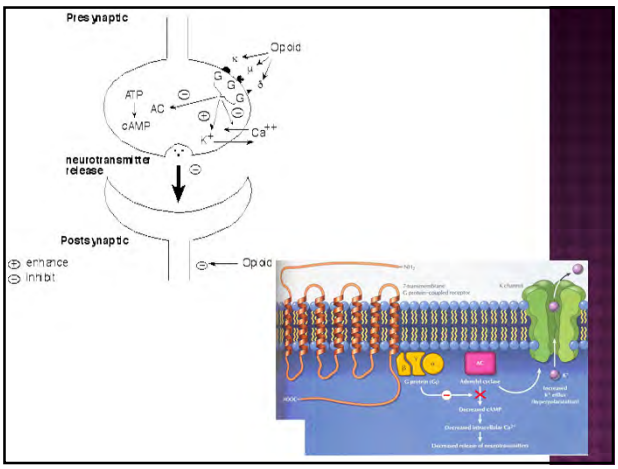
1. Acute severe pain
2. Moderate to severe chronic pain
3. Diverse pain syndromes

OPIOID RECEPTORS

- Linked to G protein
- Inhibit adenyl cyclase
- Opening of potassium channels: hyperpolarisation – reduction in neuronal excitability
- Inhibit opening of calcium channels: inhibit transmitter release

SITE OF ACTION

- Activate descending pathway
- Inhibit transmission in dorsal horn
- Inhibit excitation of sensory nerve terminals in the periphery



OPIOID RECEPTORS

Receptor	Effect
μ1	Analgesia, euphoria
μ2	Constipation, respiratory depression
Sigma	Peripheral analgesia
kappa	Analgesia and sedation on spinal level
Delta	Anxiety, hallucinations, nightmares

MORPHINE

- "Gold standard"
- IVI, IMI, oral, spinal, transdermal patch
- Metabolized by glucuronidation, N-dealkylation , and oxidation
- M-3-G and M-6-G (active)
- Excreted in bile (entero-hepatic circulation) and urine
- Dose: 0,1 mg/kg IVI/IMI

CLASSIFICATION

- Natural opioids: **Morphine**
- Semi synthetic: **Heroin**
- Synthetic: **Pethidine**
- Non analgesic derivatives: **Diphenoxylate, Loperamide, Dextromethorphan**

PHARMACOLOGICAL ACTIONS

- Analgesia
- Euphoria
- Sedation
- Respiratory depression – increase in PCO2
- Depression of cough reflex
- N+V – stimulation of CZT
- Pupil constriction – stimulation of oculomotor nucleus

CLASSIFICATION

Full agonist	Partial agonist	Competitive antagonist
• Morphine • Pethidine • Methadone • Codeine • Propoxyphene • Fentanyl	• Pentazocine • Tilidine • Buprenorphine • Nalbuphine • Tramadol • Nalorphine	• Naloxone • Naltrexone • Nalmefene

ACTIONS CONT.

- Increases tone and reduces motility of GIT
- Constipation
- Rise in intrabiliary pressure
- Acute urine retention
- Increased ICP
- Histamine release

ALTERNATIVES TO MORPHINE

- Allergy
- Lack of efficacy
- Intolerable side effects
- Change in pt status
- Practical considerations

CONTRA INDICATIONS

- Myxoedema
- Liver failure
- Kidney failure
- Status asthmaticus
- Head injuries
- Late stage of labour
- Alcoholism
- Acute abdomen

TOLERANCE AND DEPENDENCE

- **Tolerance** – increase in dose needed to produce a given pharmacological effect
- Hallmark: decrease in duration of analgesia per dose
- **Dependence** – physical (ass with withdrawal) and psychological (craving)

DIAMORPHINE

- Heroin
- Diacetylmorphine
- Analgesic
- Great addictive potential
- Crosses BBB rapidly

INDICATIONS

- **Acute pain**

1. Post op
2. MI
3. Trauma
4. Renal/biliary colic

- **Chronic pain**

1. Cancer
2. Post herpetic neuralgia

HEROIN OD

- Injected, snorted, smoked, taken orally
- Combined with **amphetamines, cocaine, marijuana**
- Substances used to dilute illicit opiates may be toxic – talc, quinine
- Opioid abuse accounts for 3.8 - 5.1% of ED presentations
- Look for needle tracks

HEROIN OD

- Pin point pupils
- Respiratory depression
- Coma
- Seizures
- Hypotension, Bradycardia
- Ventricular arrhytmias

PETHIDINE

- No pupil constriction, histamine release or suppression of cough
- Vagolytic
- Antimuscarinic action
- Metabolite: norpethidine is proconvulsant
- Dependence
- Serotonin syndrome if combined with SSRI and tramadol
- Do not combine wit MAOI

COMPLICATIONS

- Pulmonary oedema
- Rhabdomyolysis
- Renal failure
- Brain abscesses
- Mycotic aneurysm
- Pulmonary emboli
- Infective endocarditis
- HIV
- Hepatitis B

FENTANYL, ALFENTANIL, SUFENTANIL

- 75-200 times more potent than Morphine
- Short acting
- Used for severe pain or adjunct to anaesthesia
- Transdermal patch, spinal, PCA
- CVS stable
- No histamine release

MANAGEMENT

- ABC
- Naloxone vs intubation
- **Naloxone:** 0,4 mg IVI every 2-3 minutes until rousable
- IMI, via ET tube, intralingually
- Duration of action very short

METHADONE

- Longer acting, less sedating
- Rx drug dependence
- Reduces craving by occupying opioid receptor, reduces “buzz” from any additional dose taken
- Slow onset of action – reduces reward and reinforcement of dependence
- Longer t ½ - reduces intensity of withdrawal

CODEINE

- Methyl ether of Morphine
- 10% of its analgesic potency
- Combined with **Paracetamol and Ibuprofen** for moderate pain
- Cough suppressant
- Symptomatic relief of diarrhea

BUPRENORPHINE

- Partial agonist
- Antagonizes effect of full agonist – pain, withdrawal
- Rx of opiate withdrawal as alternative to **Methadone**

TRAMADOL

- Oral, IMI, IVI
- Atypical opioid
- Weak agonist at μ receptor
- Inhibits neuronal uptake of NA and serotonin – enhances gate mechanism
- No release of histamine
- Avoid with **5HT3 antagonists**
- Serotonin syndrome if combined with **SSRI**
- Not for children <12 yrs

NALBUPHINE

- Agonist at normal therapeutic dosage
- At higher dosage – antagonistic activity
- Flat-dose response curve

PENTAZOCINE

- Partial agonist
- "ceiling effect" for side effects and analgesia
- Hallucinations
- Not first line drug for severe pain

TILIDINE

- Nortilidine metabolite responsible for analgesia
- Not under 1 yr
- Dose: 1 mg/kg
- 1 drop=2,5 mg

NALOXONE

- On its own has very little effect in normal subjects
- Competitive antagonist at μ receptors
- No analgesic effects
- 0,8 – 2 mg IVI
- Used to Rx OD
- Short t ½ - may repeat dose or start infusion
- Can cause opioid withdrawal

OPIOID SELECTION: POOR CHOICES FOR CHRONIC PAIN

- Pethidine: poor absorption, toxic metabolite
- Propoxyphene: poor efficacy, toxic metabolite
- Mixed agonists-antagonists: withdrawal, ceiling for analgesia

NALTREXONE

- Longer acting
- Reduce risk of relapse in former opioid addicts

ROUTES OF ADMINISTRATION

- Oral
- Transdermal
- Transmucosal
- Parenteral
- Sublingual
- Spinal/epidural

MEDICATION SCHEDULE

- Round the clock medication
- PRN medication
- Premedication for procedures

DOSING IN CHRONIC PAIN

- Depends on prior opioid exposure, age, comorbidities, pain
- Increase dose until adequate pain relief or intolerable side effects
- If rescue (breakthrough) drug used, dose is usually 5-15% of total dose

NSAIDS

INFLAMMATION

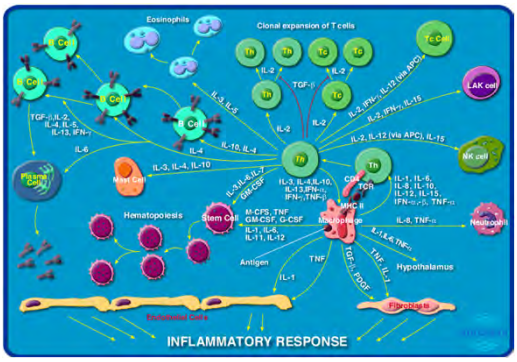
- Multifactorial
- Complex
- Interactions at multiple levels

INFLAMMATION

- Acute inflammatory reaction: event that occurs in tissues in response to an invading pathogen/ noxious substance
- Non adaptive response
- Adaptive immune response

CELLS INVOLVED IN INFLAMMATION

- Vascular endothelial cells
- Mast cells
- Tissue macrophages
- Platelets
- Leucocytes



MEDIATORS OF INFLAMMATION

1. Immunoglobulins and complement
2. Acute phase response
3. Prostaglandins and leukotrienes
4. PAF
5. Neuropeptides
6. Myeloid growth factor
7. Chemokines
8. Cytokines
9. NO
10. Angiogenesis

IMMUNE RESPONSE

- B cells – humoral immune response
- T cells – cell mediated immune reaction

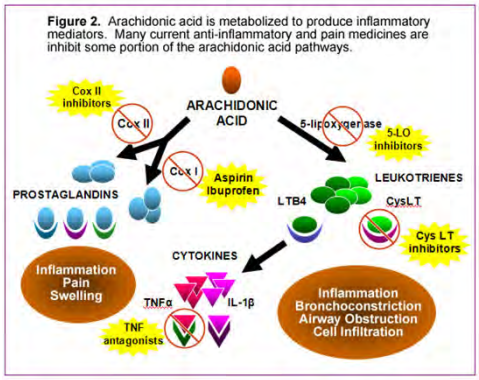


Figure 2. Arachidonic acid is metabolized to produce inflammatory mediators. Many current anti-inflammatory and pain medicines are inhibit some portion of the arachidonic acid pathways.

MEDIATORS

Leukotrienes	Prostaglandins
Bronchial and gut smooth muscle contraction	Fever
Act as chemoattractant	Pain
Act slower	Oedema
Produced by mast cells and basophils	Increased vascular permeability
	Regulate leukocyte function
	Act within seconds
	Produced by mast cells

NON OPIOID ANALGESICS

- Paracetamol
- Aspirin
- Traditional NSAIDs
- COX2 inhibitors

CYCLO OXYGENASE

COX 1	COX 2
Housekeeping enzyme – physiological function	Inflammatory function
Protects stomach mucosa	Induced by inflammatory stimulus in inflammatory cells
Regulates kidney perfusion	Lung tissue of asthmatics
Platelet aggregation	Colorectal malignancies

CLASSIFICATION OF NSAIDS

- **Salicylic acid**
- **Non selective COX inhibitors**

1. Ibuprofen
2. Indomethacin
3. Diclofenac
4. Piroxicam

- **Selective COX2 inhibitors**

1. Coxflam
2. Meloxicam

- **Specific COX2 inhibitors**

1. Coxib derivatives

NSAIDS: PROPERTIES

- Non specific analgesia
- Dose dependent effects, with ceiling dose
- Marked individual variation in response to different drugs

ANTIPYRETIC

- Interleukin-1 releases prostaglandins in CNS. These increase hypothalamic set point for temperature control, leading to fever.
- NSAIDs prevent this

NSAIDS

- Anti-inflammatory
- Analgesic
- Antipyretic
- Antiplatelet

ANALGESIC

- Pain associated with inflammation or tissue damage
- Reduction in prostaglandins leads to less sensitisation of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5HT
- Headache relieved due to a reduction in prostaglandin mediated vasodilatation

ANTI-INFLAMMATORY

- Vasodilatation
- Oedema
- COX inhibitors have no effect on processes (lysosomal enzyme release, toxic oxygen radical production) that contribute to tissue damage in chronic inflammatory conditions

ADVERSE EFFECTS OF NSAIDS

- **GIT:** gastritis/gastric mucosal erosions and bleeding, dyspepsia, diarrhoea, N+V
- **Skin:** 10-15% with **Mefenamic acid** – rash, urticaria, photosensitivity
- **Airways:** bronchospasm in aspirin sensitive asthmatics
- **Heart:** cardiac failure, MI
- Antagonize effects of antihypertensive Rx
- Reduce Lithium clearance

CONT.

- **Kidneys:** vasoregulatory renal impairment, hyperkalaemia, interstitial nephritis, nephrotic syndrome, analgesic nephropathy, renal papillary necrosis
- **Liver:** biochemical hepatitis
- Bone marrow disturbances

PRECAUTIONS

- Elderly are more prone to adverse effects
- Hypersensitive to one NSAID – cross reactivity to another NSAID
- Administer with food
- Concomitant use of alcohol will aggravate gastric irritation
- Caution in pt with hypertension, cardiac failure, angina and renal impairment
- Dehydration during NSAID use enhances risk of renal damage

INDICATIONS

- Pain and swelling of chronic joint disease
- Acute inflammatory conditions
- Fractures
- Sprains
- Soft tissue injuries
- Headache/ migraine
- Dental pain
- Menstrual pain
- Post operative

DRUG INTERACTIONS

- ACE inhibitors: NSAIDs block production of vasodilator prostaglandins
- Steroids: risk of GI ulceration
- Warfarin: risk of bleeding

CONTRA-INDICATIONS

- Hypersensitivity
- Active peptic ulceration

ASPIRIN

- Irreversible inactivation of COX1
- Inhibits platelet aggregation
- Inhibits PGE synthesis- loss of gastric protection
- Inhibits PGI synthesis – vasodilatation , platelet aggregation inhibited
- Used for prevention and treatment of MI, CVI

KINETICS

- Absorbed from small intestine
- T½ = 30 minutes
- Pka = 3,5
- Hydrolysed to salicylic acid
- Clearance dosage dependent (first order followed by zero order)
- Excreted as salicylic acid, partially conjugated to glycine and glucuronic acid
- Glycine conjugation saturated with OD
- Actively excreted by anionic pump in proximal kidney tubules and partially reabsorbed by reabsorption carriers

ADVERSE EFFECTS

- Allergic reaction
- Reye's syndrome: acute encephalopathy and fatty change in liver

SIDE EFFECTS

- Tinnitus
- Gastric erosions
- GIT bleed – prevent by: buffered Aspirin, dissolving in water, Diflusinal

DRUG INTERACTIONS

- Increases effect of **Warfarin**
- Interferes with **Probenecid and Sulfinpyrazone**

POISONING

- Metabolic acidosis
- Respiratory alkalosis
- Tinnitus
- Vertigo
- N+V
- Dehydration
- Disorientation, delirium
- Bleeding occurs later
- Hyperthermia
- Rx: forced alkaline diuresis or haemodialysis

PARACETAMOL

- Oral, IVI, suppository
- Metabolite of Phenacetin
- Analgesic and antipyretic
- Not anti-inflammatory
- Selective inhibitor of COX3
- Allergic skin reaction may occur
- Risk of kidney damage

OD MANAGEMENT

- Take blood levels
- Rx: **N-acetylcysteine**
- IVI: 150mg/kg in 200ml 5%Dextrose over 15 min, 50mg/kg in 500ml 5%Dextrose over 4 hours, then 100mg/kg in 1L 5%Dextrose over 16 hours
- Give within 8 hours of ingestion
- NAC precursor to glutathion- increasing availability to bind NAPQI
- **Methionone** other option

PARACETAMOL OD

- Toxic dose after single ingestion of 150mg/kg or 7g in adults
- **NAPQI** (N-acetyl-P-Benzoquinone –imine) formed- toxic metabolite
- NAPQI binds to proteins and lipid bilayer of hepatocyte membrane, leading to hepatocellular death and centrilobular liver necrosis

INDOLE DERIVATIVES

- **Indomethacin**
- Powerful anti inflammatory agent
- Weak analgesic
- RA, AS, gout
- SE: confusion, hallucinations (crosses BBB)

PARACETAMOL OD

- Initially asymptomatic
- N+V
- Malaise
- Increase in serum transaminase
- Jaundice
- Hypoglycaemia
- Coagulopathy
- Encephalopathy
- Renal failure

PROPIONIC ACID DERIVATIVES

- **Naproxen, Fenoprofen, Ibuprofen, Ketoprofen**
- Weak anti inflammatory
- Fewer SE
- **Naproxen** can have drug interactions with **sulphonylureas and anti coagulants**

FENAMIC ACID DERIVATIVES

- **Mefenamic acid (Ponstan®), Meclofenamic acid**
- Used for Rx of dysmenorrhea
- Not to be used for longer than 5 days
- Not in children < 6 months or < 10 kg
- Potentially nephrotoxic
- SE: diarrhea

COXIBS

- **Celecoxib (Celebrex®), Etoricoxib (Arcoxia®), Parecoxib (Rayzon®)**
- Specific COX2 inhibtors
- Less gastro toxic
- Same effect on renal function
- Contain sulphonamides – risk of hypersensitivity
- Increased risk of CVS events – some drugs removed from market
- Not in children < 18 yrs

PHENYLACETIC ACID DERIVATIVES

- **Diclofenac (Voltaren®)**
- Oral, drops, IMI, suppository
- Not in children < 2 yrs
- Deep IMI injection can lead to irreversible neural damage
- Suppositories can cause proctitis
- Not be taken for longer than 5 days

OTHER

- **Ketorolac (Tora-dol®)**
- Powerful analgesic, moderate anti inflammatory
- Oral, IMI, IVI, topical in eye
- Post op pain
- Not in children < 16 yrs
- Not longer than 5 days

OXICAMS

- **Tenoxicam, Meloxicam, Lornoxicam**
- Longer acting
- Not in children < 18 yrs

CLASSIFICATION

Group I – simple analgesic , no anti-inflammatory action

- Low dose Aspirin
- Paracetamol
- Propoxyphene
- Codeine

Group II – slight anti-inflammatory action

- Ibuprofen
- Ketoprofen
- Mefenamic acid

CLASSIFICATION

Group III – moderate anti-inflammatory action

- Diclofenac
- Meloxicam
- Celecoxib

Group IV – strong anti-inflammatory action

- High dose Aspirin
- Indomethacin
- Phenylbutazone

TREATMENT OPTIONS

Pain source	Potential analgesics
Trauma/post op/ post procedure	Opioids, NSAIDs, epidural
Exacerbation of sickle cell/cancer pain	Opioids, NSAIDs, steroids, adjuvants
Chronic lower back pain	NSAIDs, muscle relaxants, opioids
Diabetic peripheral neuralgia	Antidepressants, anticonvulsants, capsaicin
Trigeminal neuralgia	Carbamazepine, baclofen
Post herpetic neuralgia	Antidepressants, pregabalin
Cancer/HIV	Combination

NSAID WITH OR WITHOUT OPIOIDS?

- Combination effective in acute pain
- Reduction in side effects in acute pain

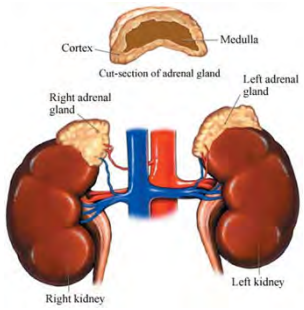
GLUCOCORTICOSTEROIDS

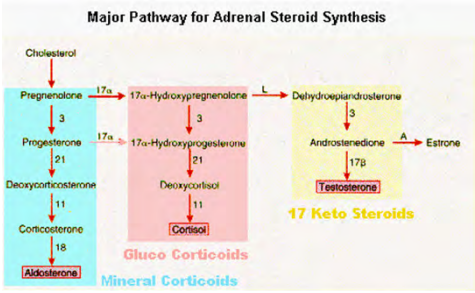
WHICH NSAID NOT TO CHOOSE?

- No gold std
- GI concerns: aspirin, indomethacin
- Renal impairment: ketorolac
- CNS: indomethacin
- Liver: paracetamol
- Bleeding: aspirin

ADRENAL CORTEX

- Glucocorticosteroids
- Mineralocorticoids
- Androgens



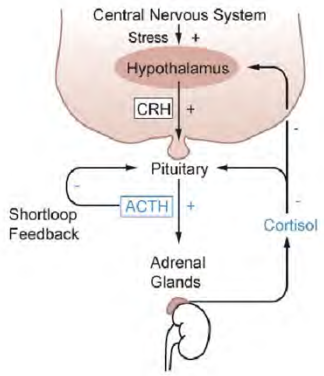


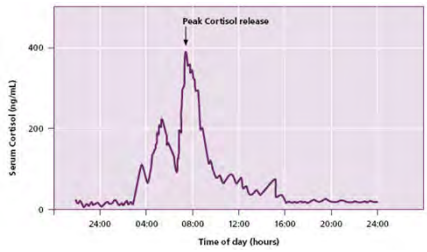
FEEDBACK LOOPS

- External stimuli
- Hypothalamus
- Anterior pituitary
- Adrenal cortex
- Tissues

GLUCOCORTICOSTEROIDS

- Not stored
- Rate of synthesis= rate of release
- Synthesis controlled by irregular pulses of ACTH
- Influenced by light
- Major pulse early morning





MECHANISM OF ACTION

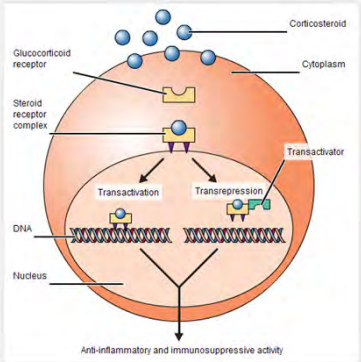
- All steroids stimulate the transcription of selected genes
- These genes then mediate the synthesis of particular proteins, which bring about cellular effects

MECHANISM OF ACTION

- At steroid sensitive tissue there is a specific corticosteroid binding protein receptor in cytoplasm
- Steroid will activate the receptor – exposing a DNA binding domain- moves to nucleus and steroid-receptor-protein complex binds with DNA
- Increase in RNA polymerase activity, forming specific messenger RNA
- Polypeptide synthesis follows
- Lipocortin- inhibitor of phospholipase A2

ACTIONS OF CORTISOL

1) Effect on fluid and electrolyte balance, fat, carbohydrate and protein metabolism
2) Anti-inflammatory and immunosuppressive
3) Feedback



CARBOHYDRATE, FAT AND PROTEIN METABOLISM

- Enhances gluconeogenesis
- Antagonizes insulin
- Hyperglycaemia
- Hypertriglyceridaemia
- Hypercholesterolaemia
- Decreased protein synthesis, and increase in breakdown of protein

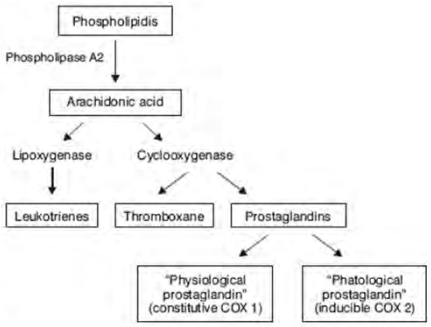


Figure 1 - Mechanism of action of nonsteroidal anti-inflammatories

WATER AND SALT METABOLISM

- Sodium and water retention
- Potassium loss
- Increased renal loss of calcium

ANTI-INFLAMMATORY ACTION

- Inhibits PAF, TNFα, prostaglandins, and leukotrienes
- Reduction in proliferation of T cells and migration of inflammatory cells
- Cell mediated immunity is impaired and antibody production suppressed

ALIMENTARY

- Increased production of gastric acid and pepsin

FEEDBACK

- Inhibits release of ACTH and MSH

USES

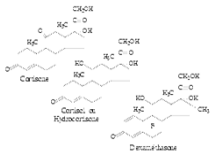
- Adrenal insufficiency
- Asthma
- Allergic rhinitis
- Sarcoidosis
- SLE,RA
- Autoimmune inflammatory diseases
- Eczema
- Oncotherapy and organ transplantation
- Nephrotic syndrome
- Liver diseases
- Brain oedema

HAEMATOLOGICAL

- Lowers lymphocytes and eosinophil count
- Increases neutrophils, platelets and clotting tendency

DRUGS

- Oral: **Prednisone, Prednisolone**
- IVI: **Hydrocortisone**
- Aerosol: **Budesonide, Beclometasone, Fluticasone**
- Topical: **Hydrocortisone**



RELATIVE POTENCIES

Compound	Anti-inflammatory	Mineralocorticoid
Glucocorticosteroid		
Hydrocortisone	1	1
Cortisone	0.8	1
Prednisolone, prednisone	4	0.8
Dexamethasone	25-30	0
Betamethasone	25-30	0
Mineralocorticosteroid		
Aldosterone	0	1000
Fludrocortisone	10	500

DEXAMETHASONE

- Powerful anti-inflammatory action
- Diagnostic agent in Cushing's syndrome
- Cerebral oedema
- Combined with anti-emetics
- Pregnant mothers

HYDROCORTISONE

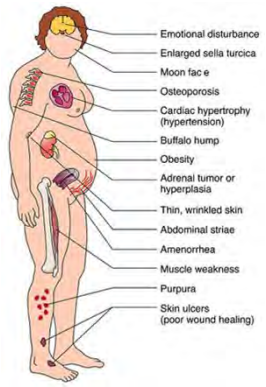
- Replacement therapy in adrenal insufficiency
- Acute severe asthma
- Autoimmune inflammatory disease
- Hydrocortisone acetate suspension injected into joints
- Presystemic metabolism
- Metabolized by CYP3A
- Plasma t½ is 90 minutes, but biological t½ is longer (6-8 hours)

GLUCOCORTICOSTEROID SIDE EFFECTS

- CNS: depression to mania
- Glaucoma
- Skin: thin, bruising, striae, hirsutism and acne (androgen metabolism)
- Atrophy of muscles and bones (osteoporosis)
- Hyperglycaemia
- HT, CCF, oedema
- Peptic ulcers
- Potassium loss: muscle weakness
- Release of antigrowth hormone
- Redistribution of fat
- Susceptible

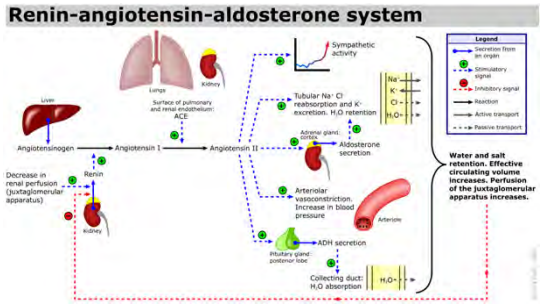
PREDNISOLONE

- More potent anti-inflammatory action
- Connective tissue diseases
- Asthma
- Sarcoidosis
- Nephrotic syndrome
- Liver disease



CHRONIC THERAPY

- Once daily or alternative days, to reduce adrenal suppression
- Slow-dose tapering to prevent adrenal crisis
- Increase dose for stresses: infection or surgery



MINERALOCORTICOSTEROIDS

- Aldosterone
- Fludrocortisone

FLUDROCORTISONE

- Synthetic mineralocorticoid
- Mimics action of aldosterone by binding to mineralocorticoid steroid receptor
- Replacement therapy in adrenal insufficiency

ALDOSTERONE

- Secreted by zona glomerulosa of adrenal cortex
- No glucocorticoid activity
- Sodium retention
- Urinary loss of potassium and hydrogen ions

CASE STUDY

CASE STUDY

- 34 yrs old female presents to casualty after falling off her bicycle. She is healthy and on no medication.
- History of one episode of acute arthritis in right big toe that responded to NSAIDs but caused severe gastritis.
- Diagnosed with soft tissue injuries and multiple rib #
- Stable but a lot of pain

TRUE OR FALSE

1) Opioids bind to μ receptors
2) Opioids bind D2 receptors
3) Opioids bind to 5HT receptors
4) Cyclosporin is an opioid agonist drug
5) Codeine is an opioid agonist drug
6) Cetirizine is an opioid agonist drug
7) Constipation is not a potential SE of opioid agonists
8) Nausea is not a potential SE of opioid agonists
9) Midriasis is not a potential SE of opioid agonists

CASE STUDY

- Discuss pain management for this patient and motivate why you would and would not use certain drugs.

TRUE OR FALSE

1) GC are indicated for the Rx of eczema
2) GC are indicated for the Rx of asthma
3) GC are indicated for the Rx of osteoporosis
4) Hypoglycaemia is a SE of long term use of GC
5) Easy skin bruising is a SE of long term use of GC
6) HT is a SE of long term use of GC
7) Cortisol is not stored
8) Cortisol is controlled by ACTH feedback
9) Cortisol has a major pulse early in the morning
10) GC increase RBC and Hg content
11) GC increase circulating lymphocytes
12) GC block the production of prostaglandins

TRUE OR FALSE

1) NSAIDs inhibit the Cox enzyme and its isoforms COX1 and COX2
2) NSAIDs promote the synthesis of prostaglandins
3) Morphine is an example of a NSAID
4) COX1 isoform is expressed in most tissues
5) COX1 isoform plays a housekeeping role
6) COX2 isoform is responsible for production of inflammatory cytokines
7) NSAIDs improve renal blood flow
8) NSAIDs are used to treat gastric ulcers
9) NSAIDs have anti-inflammatory and analgesic properties

ANY QUESTIONS?