ANALGESIC DRUGS & PHARMACOLOGY

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Basisprincipes pijnbestrijding

- By the clock
  - Onderhoudsbehandeling volgens vast schema
  - '**Noodmedicatie**' (doorbraak) beschikbaar en snelwerkend
    - Van allergrootste belang bij wondverzorging!
    - Soms ook pre-emptief (voor verzorging) toe te dienen
- By the patient
  - Rekening houden met individuele kenmerken van elke patiënt en zijn/haar voorgeschiedenis
  - Type van pijnklacht in rekening te brengen
- By the ladder
  - Vervangen door lift…bij uitgebreide wonden …
  - Elk analgeticum op correcte wijze doseren!

Regelmatige evaluatie

- Analgetisch effect
  - Voldoende tijd in acht nemen ($t_{1/2}$)
    - Cave: NASID's, methadon, …
  - Verschillende doseringen testen
  - Multimodale aanpak van pijnklacht
    - Combinatie van analgetica/behandelmethoden met verschillend werkingsmechanisme
- Neveneffecten
  - Steeds afweging maken van pro's en con's
  - Intensiteit/ernst (en duur) neveneffecten !

TYPE van pijnklacht

- Somatische pijn
  - Bot, ligamenten, spieren
- Viscerale pijn
  - Holle organen
- Neuropathische pijn (niet-nociceptieve pijn)
  - Letsel of beschadiging in het zenuwstelsel
- *(Neuroplastische pijn)*
  - Veelal veralgemeende pijnsyndromen

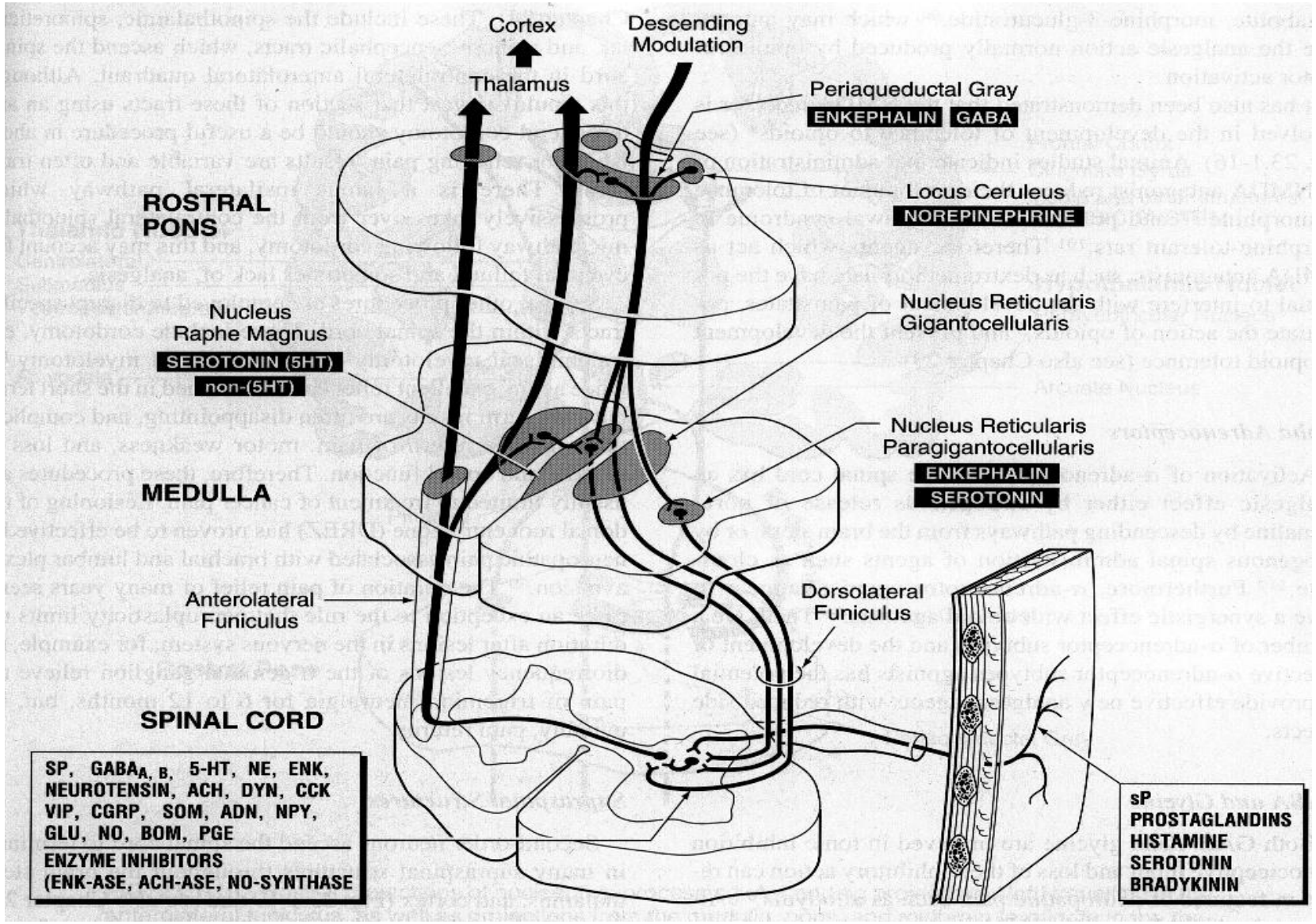
Pijnanamnese

- P
  - Palliative and provoking factors
- Q
  - Quality of the pain
- R
  - Radiation of pain symptoms
- S
  - Severity
- T
  - Timely factors

Adjuvantia !

- Toenemende rol in hedendaagse pijnbestrijding
  - Opioid sparend
  - Betere werkzaamheid tegen bepaalde pijntypes
    - Oa. neuropathische pijn
- Interactie met specifiek “target”
  - Descenderende inhiberende banen
  - Dorsale hoorn
  - Corticale strukturen

Afferent and Descending Pathways



ANALGESIC LADDER or ELEVATOR

1. Non-Opioid Analgesics
Plus Adjuvant Drugs

Aspirin
Paracetamol
NSAIDs

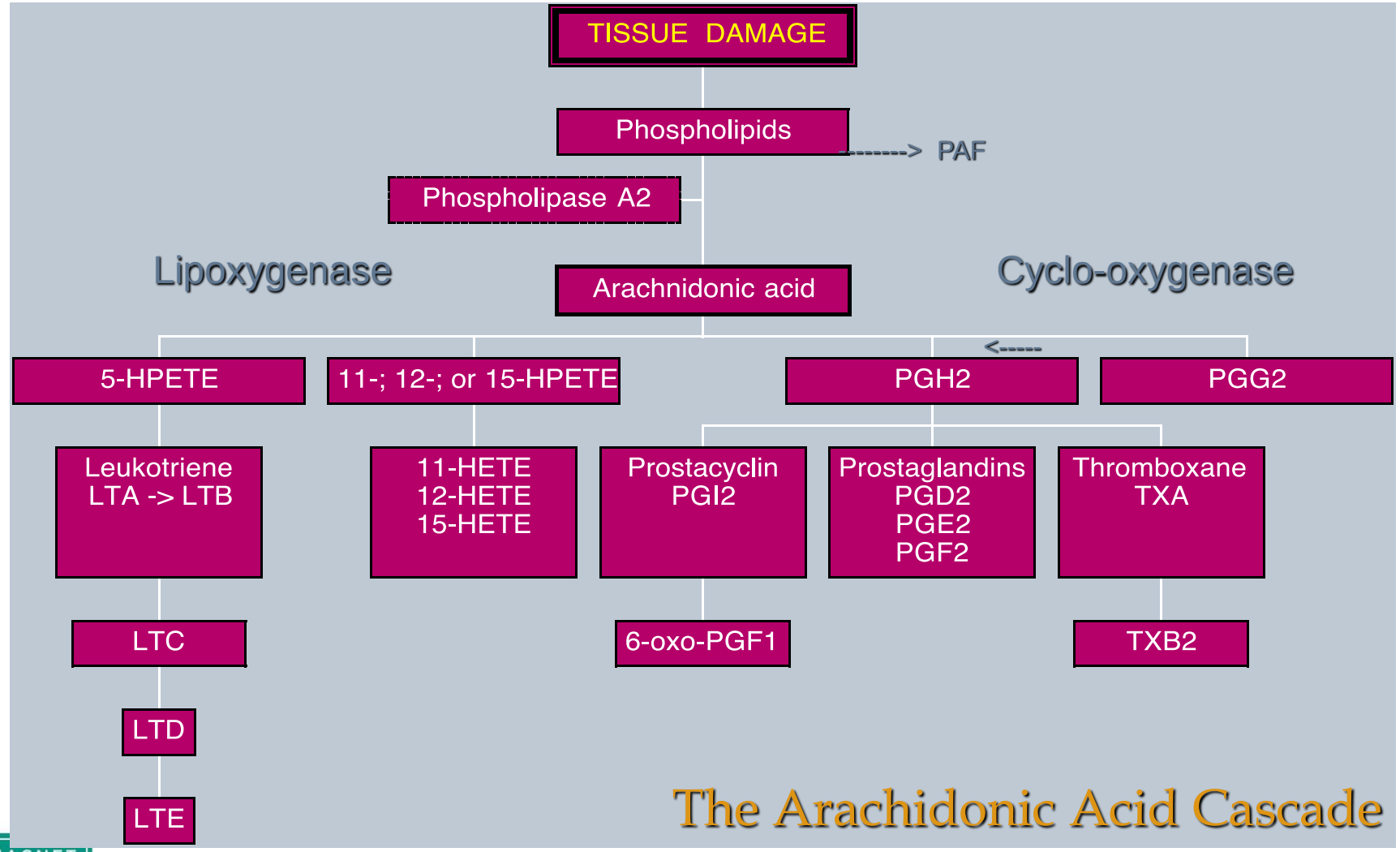
2. 'Weak' Opioid Analgesics
Plus Non-Opioid Analgesics
Plus Adjuvant Drugs

Codeine
~~D-propoxyfeen~~
Hydrocodeine
Tramadol
Buprenorfine ?

3. 'Strong' Opioid Analgesics
Plus Non-Opioid Analgesics
Plus Adjuvant Drugs

Morphine
Oxycodone
Methadone
Piritramide
(TTS-)Fentanyl
Tapentadol

Peripheral Antinociceptive Modulation by NSAIDs (1)



Peripheral Antinociceptive Modulation by NSAIDs (2)

- Inhibition of *Cyclo-Oxygenase*
  - (at least) 3 distinct categories of inhibitors
    - Reversible competitive inhibition
      - Ibuprofen; piroxicam
    - Reversible non-competitive inhibition
      - Paracetamol
    - Irreversible inactivation
      - Aspirin, indomethacin

Peripheral Antinociceptive Modulation by NSAIDs (3)

- Inhibition of *Lipoxygenase*
  - LTB and 12-HETE present in inflammation
    - Chemotactic action on leucocytes
      - Lower firing threshold of pain fibers
      - Stimulate nociceptors
    - Diclofenac; Indomethacin
- *Non-prostaglandin* Inhibitory Actions
  - Interference with cell membrane processes
    - Piroxicam; Indomethacin

Central Antinociceptive Modulation by NSAIDs (1)

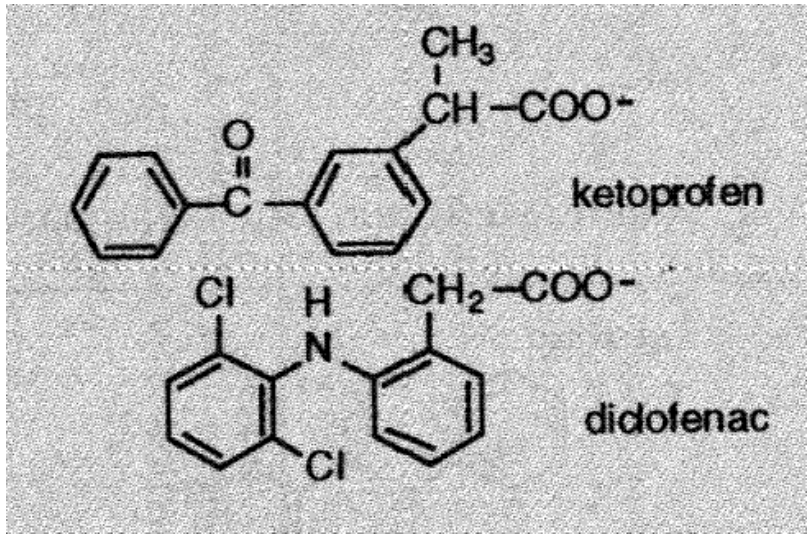
- *Central Prostaglandin Synthesis*
  - Reduction of Prostaglandins E and F in CNS
    - Diclofenac; indomethacin; naproxen, PCT
- *Opioid* Mechanisms
  - Central opioid mechanism of action
    - Diclofenac; ketorolac; lysine acetylsalicylate
      - Reversal by naloxone
    - Reduce heroin withdrawal syndrome

Central Antinociceptive Modulation by NSAIDs (2)

- *Serotonergic* Mechanisms
  - Brain stem and spinal cord
    - Serotonin and 5-hydroxyindoleacetic acid
    - Diclofenac
  - Activation of descending serotonin pathways
    - Probably through 5-HT_2 receptor system
- *NMDA* Mechanisms
  - Reduction of hyperalgesia induced by
    - Spinal glutamate or substance P receptors
    - Aspirin; ibuprofen; ketorolac

High Potency - Fast Elimination

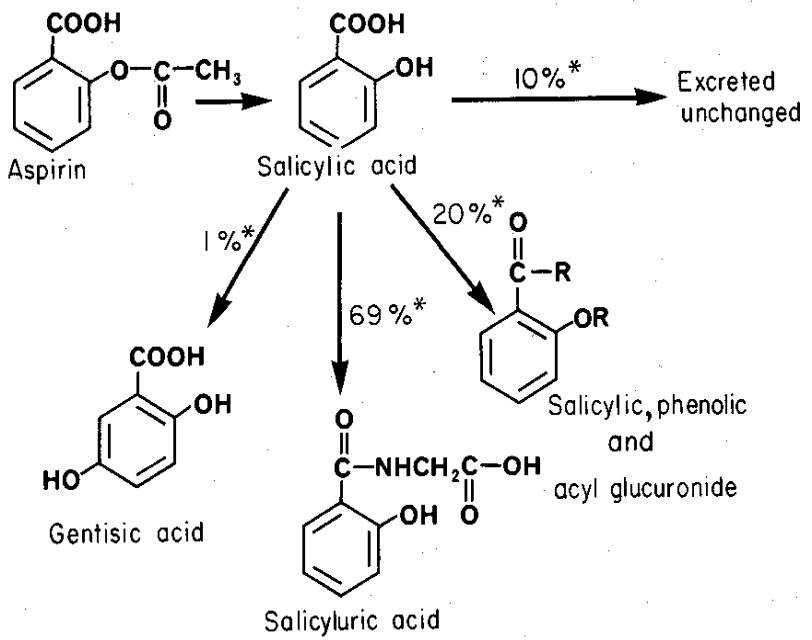
- Arylpropionic : Ketoprofen
  - Rofenid®; Rofenid Enteric®; Rofenid Long Acting®; Rofenid Retard®
  - 0.5-2h T*max*, 1.1-4h T*1/2*
  - 200mg (-300mg) daily dose
- Arylacetic acids
  - 0.5-2h T*max*, 4-10h T*1/2*
  - **Diclofenac (Voltaren,Cataflam®)**
    - Dissolve in stomach
    - Short half-life of 1 - 2 h
    - Daily dose:100 - 150 mg
  - **Ketorolac (Taradayl®)**
    - 100% bio-availability IM/PO
    - 10 - 30mg every 6-8 hours
    - 60 (elderly) to 90 mg daily dose
    - IM/IV max 2 days



No combination with other NSAIDs
Not during labor and delivery

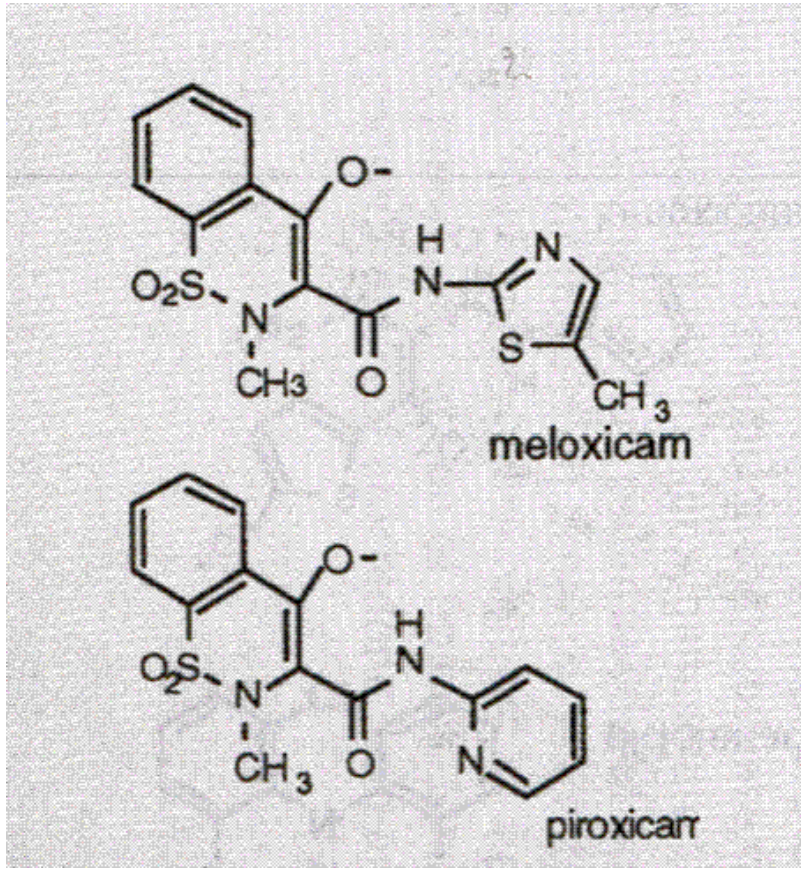
Low Potency - Fast Elimination

- **Salicylates**
  - +/- 0.25h T*max*
  - +/- 20min T*1/2*
  - Low dose (500mg, 2x/d)
    - Analgesic & antipyretic effect
  - High dose (1000mg, 3x/d)
    - Anti-inflammatory effect
  - Individual variation in absorption
    - Dosage not predictable

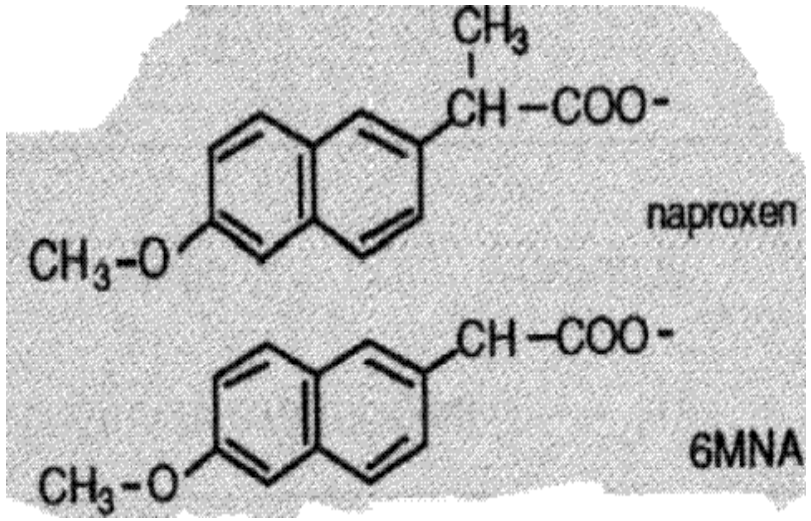


- **Lysin - acetylsalicylic acid (Aspegic®)**
  - water soluble salt, sodium free
  - 1.8g aspegic = 1.0g aspirin
  - fast absorption
  - 500 - 1000mg, 2 to 3 x /day

High Potency - Slow Elimination



- Oxicams
  - Piroxicam (Feldene®)
    - 3-5h T*max*, 35-70h T*1/2*
    - 20mg-40mg, daily dose
    - Lyotabs equal Tmax, T1/2
    - Elevated aminotransferase levels in 15%
      - Monitor liver enzymes first 8 wk
  - Tenoxicam (Tilcotil®)
    - 100% bio-availability PO
    - 3-5h T*max*, 42-98h T*1/2*
    - 20mg-40mg daily dose
    - Inhibitor of metalloproteinase
      - Degenerative bone diseases!



- Arylpropionic acids
  - Naproxen EG®; Naprosyne®
    - 2-4h T*max*
    - 12-15u T*1/2*
    - 500 - 1000mg daily dose
    - Extremely good penetration
      - Synovia
      - Inflammatory tissues
  - Apranax® *(natriumnaproxen)*
    - < 1h T*max*
    - 12 – 15u T*1/2*
    - 550 mg, 2 x day

Cyclo-oxygenase

- Physiological stimulus
  - Constitutive expressed enzyme

    COX-1

    Platelets, stomach, intestine, kidney

  - Normal cell functions "house keeping"

- Tissue damage
  - Inducible enzyme
  - Not constitutive ??

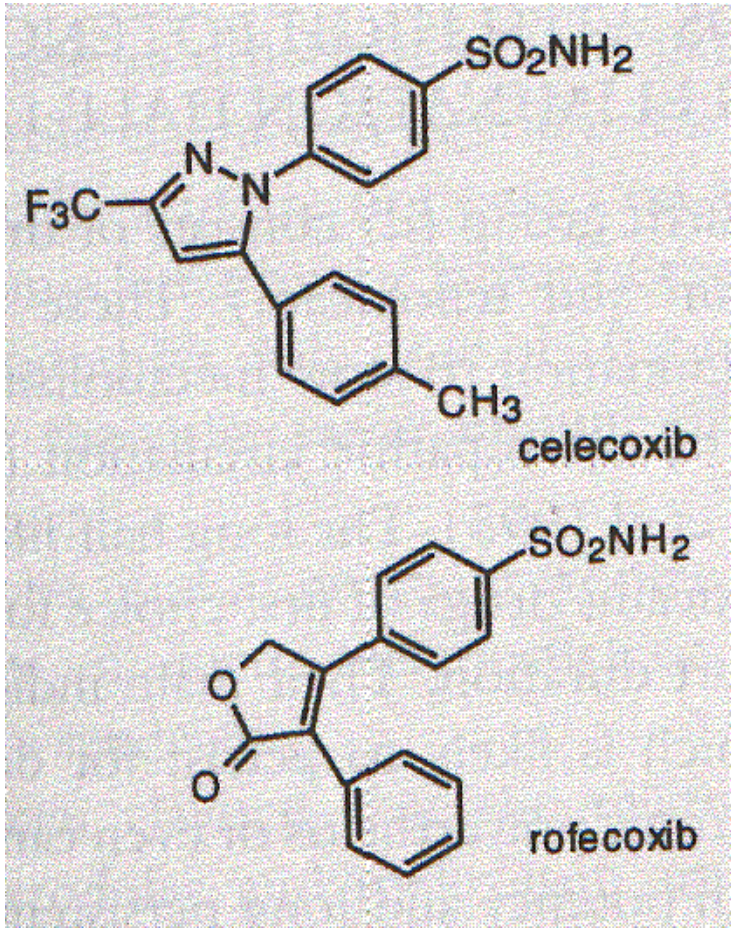
    COX-2

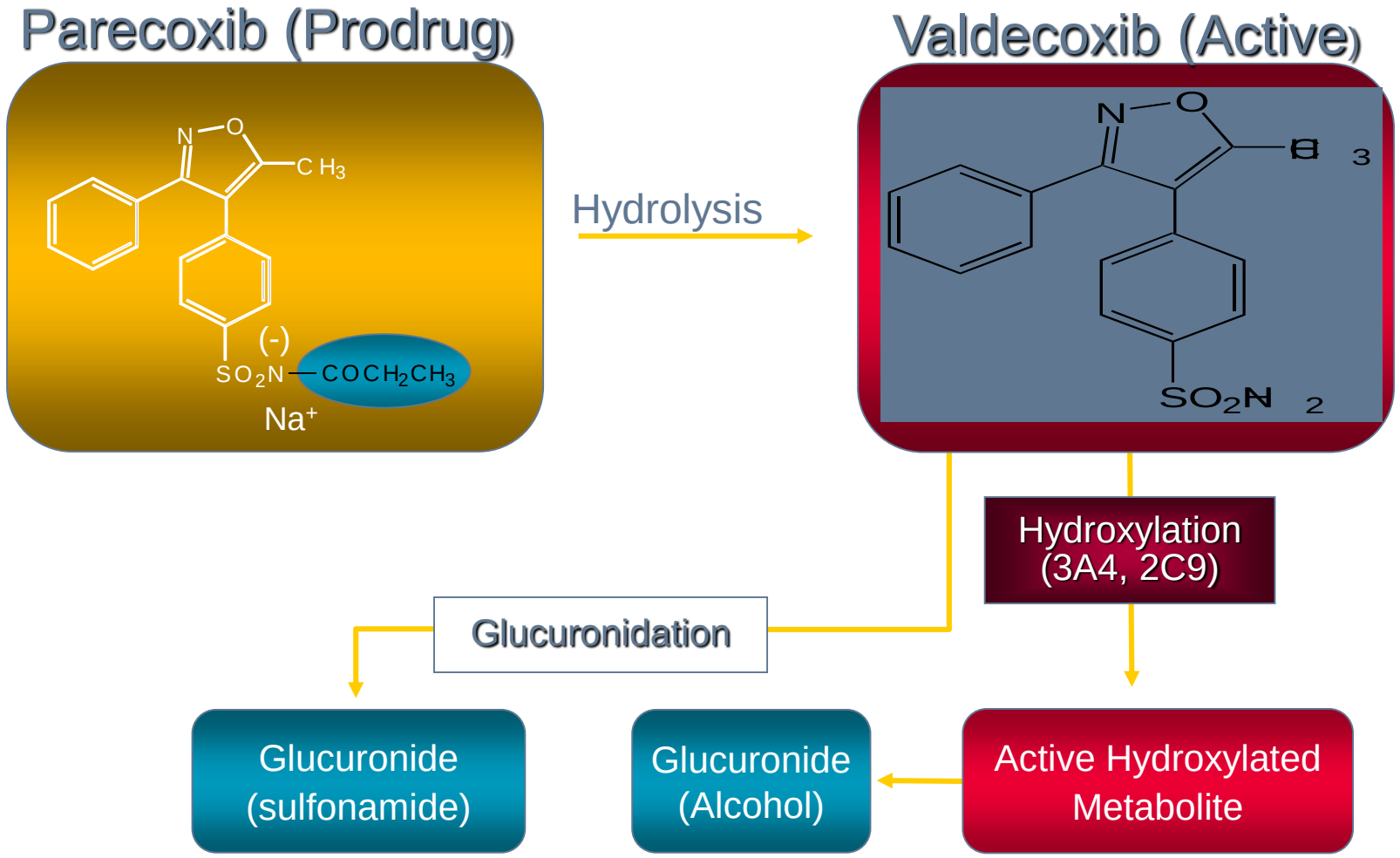
    Macrophages, synoviocytes

  - Inflammation, regulation electrolyte balance

Selective COX-2 Inhibitors

- Celecoxib (Celebrex®)
  - 2-4 h T*max*, 9-15 h T*1/2*
  - 400mg max daily dose
- Rofecoxib (Vioxx®)
  - 2-4 h T*max*, +/- 12h T*1/2*
  - 50mg max daily dose (acute conditions!)
- Valdecoxib (Bextra®)
  - 20mg max daily dose
  - no dose adjustments in elderly
- Etoricoxib (Arcoxia®)
  - faster effect
  - long-term effect (once daily)
  - no information on side effects yet
  - …





Adapted from Karim A et al. *J Clin Pharmacol.* 2001;41:1112.

COX-2 antagonisten

- **Polemiek rond mogelijks meer cardiale verwikkelingen (uit markt gehaald)**
  - Rofecoxib (Vioxx)
  - Valdecoxib (Bextra)
    - Langdurige inname (Parecoxib OK ?)
    - Hoge dosis (preventie colorectale CA?)
    - **CVA, MI, hartsdecompensatie, hypertensie, …**
- **Stevens-Johnson, leverfalen, …**
- **Ook de klassieke COX antagonisten ???**

Paracetamol (1)

- **Non-acidic antipyretic analgesic**

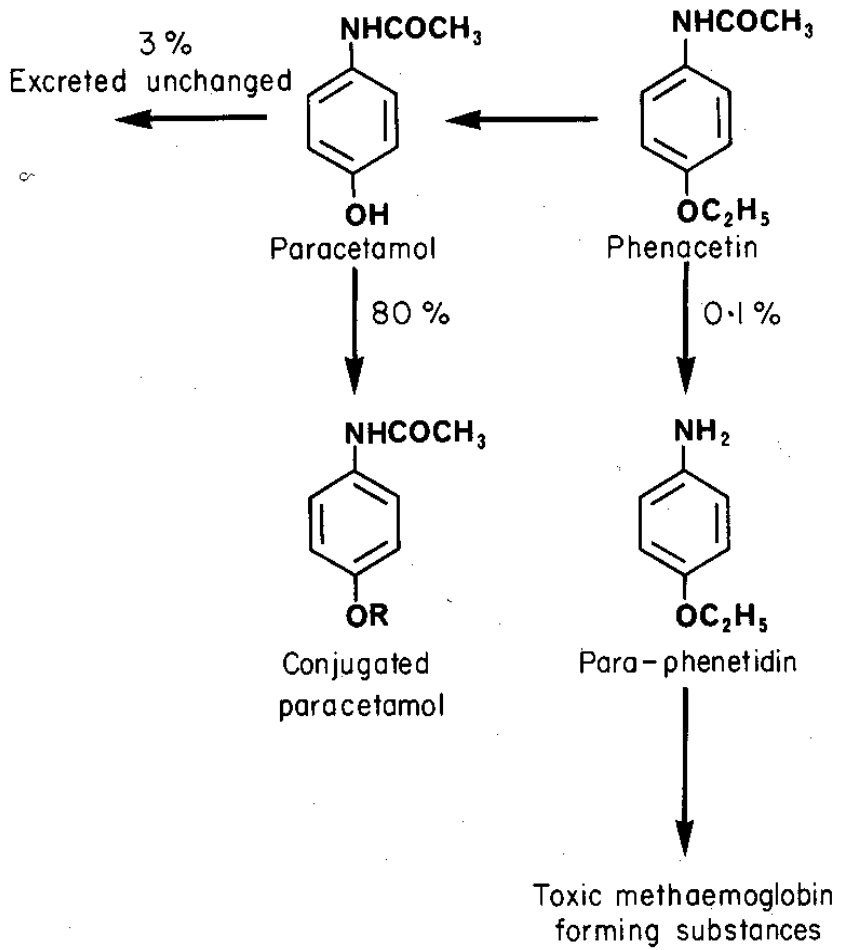
  (Dafalgan®, Perdolan Mono®; Efferalgan, Dolprone...)

  - Very weak inhibitor cyclooxygenase (central, indirect ?)
  - Strong *antipyretic* effect
  - Lacks significant anti-inflammatory property
  - Maximum analgesic effect at **1000 mg**
    - Central action (synthesis of prostaglandins)
    - Importance of high and quick peak plasma concentration
    - Dose-effect correlation in CNS
    - Ceiling of analgesic effect at 1g PO, and this 3 x day
    - Better than 60 mg Codeine and Tramadol 100 mg
    - Combinations remain possible !

Paracetamol (2)

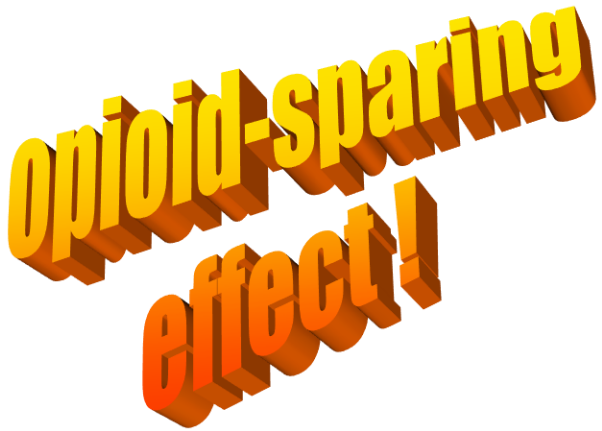
- Short term use
  - < 4 gm / day

- Long term use
  - < 3.2 gm / day
  - < 2.4 gm / day
    - Elderly
    - Debilitated persons
    - Alcohol intake
    - Malnutrition



Paracetamol (3)

- Perfusalgan (IV)
  - Different from previous Pro-Dafalgan !!
    - Pro-drug: 2:1 conversion , Mannitol
  - Concentration of 10 mg/ml
  - Water soluble form of paracetamol
  - 1:1 ratio
  - Faster onset of action
  - More efficacious
  - First day : 6g ?, 2g better than 1g ?
  - Longer duration of action
  - Slow administration (!) otherwise possible hypotension
  - Good local tolerance
    - Osmolarity and pH close to human plasma



Tramadol Hydrochloride (1)

- Synthetic, *centrally* acting analgesic

(Contramal®, Dolzam®,Tradonal®; Tramium®; ...)

- Dual mechanism of action:
  - Specific selectivity and low affinity for μ-opioid receptor
    - 6000 times less than morphine
  - Interaction with neurotransmitter transmission
    - Stimulation neuronal serotonin release
    - Inhibition pre-synaptic reuptake NA and serotonin

- Analgesic effect of <u>each</u> component is modest
  - Low incidence of certain opioid-like adverse effects
  - Low tolerance and dependence potential
- **RESPONDERS and NON-RESPONDERS ?**

Tramadol Hydrochloride (2)

- No respiratory depression in therapeutic range
- Almost no risk of constipation
- Nausea/vomiting; somnolence; transpiration
- No euphoria
- Low plasma protein binding (20%)
  - No interference other drugs (except MAO-I, 5-HT antagonisten)
  - Combination with NSAIDs allowed
- Not a non-steroidal anti-inflammatory drug
  - No anti-inflammatory activity
  - No prostaglandines side effects

Tramadol Hydrochloride (3)

- Conversion in liver to active M_1 metabolite
  - Excretion as unaltered drug and metabolites in urine
  - Low-affinity of parent compound + high-affinity binding of M1 metabolite to μ-opioid receptor
- Risk of seizures
  - Doses above recommended range
  - Decreasing seizure threshold
    - Tricyclic antidepressants
    - SSRI's
    - MAO-inhibitors

Tramadol Hydrochloride (4)

- Potency:
  - IV: 100mg tramadol = 10mg morphine
  - PO: 50mg tramadol = 10mg morphine
    - Bio-availability: tramadol 70% vs. morphine 20-25%
- Duration of 3 - 6 h ,T*max* PO 1 - 2 h; Parenteral 45 min
- Max daily dose **400mg**
  - No changes in elderly (<75 years)
  - Increase interval
    - Liver failure
      - Higher levels tramadol
      - Decreased levels of M1
    - Renal failure
      - Creatinine clearance < 30mL/min
        - 50-100mg every 12h

Tramadol + … (5)

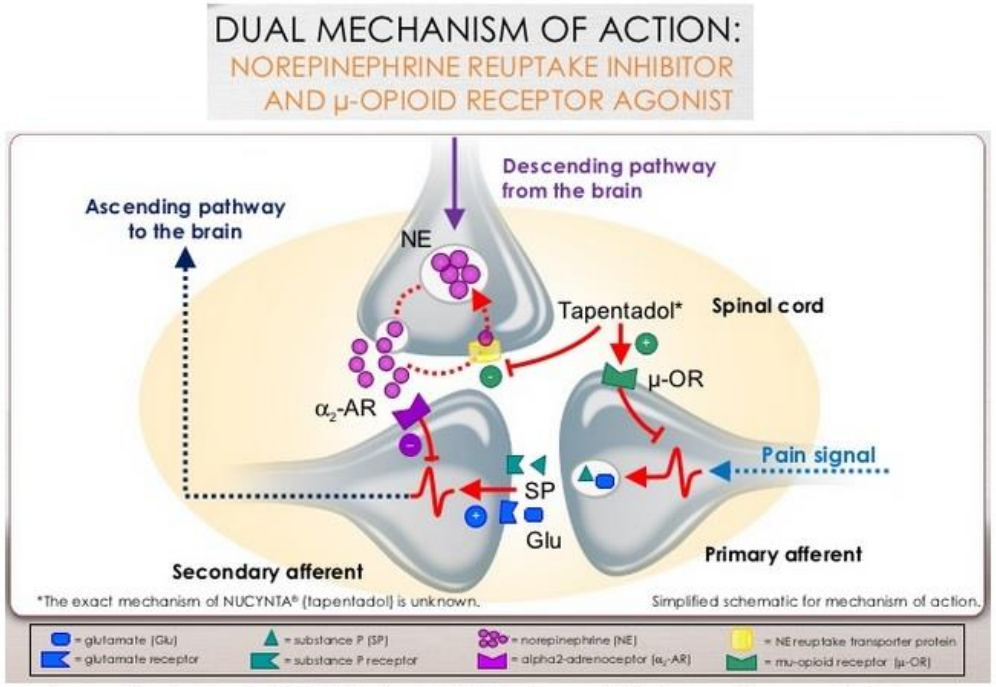
- Combination analgesic (Zaldiar®, …)
  - Paracetamol (325mg) + Tramadol hydrochl. (37.5mg)
  - The rationale for combining complementary analgesics acting by different pathways is an improved benefit/risk ratio through enhancement of analgesia (synergim or addition) and/or reduction of side effects
- No undesirable interactions when the two analgesics are given in combination as either single or repeated doses
- The time to achieve maximal plasma concentrations is about 30-60 minutes for paracetamol and 2 hours for tramadol
- Both drugs are metabolised via the liver, but each compound is broken down along separate metabolic pathways
- Cave: long-acting combinations !?

Tramadol + Dexketoprofen

- 75mg tramadol and 25mg dexketoprofen (trometamol)
- Half-life of components very different!
- 2 studies post-operative conditions, nothing in ambulatory care
- Less pain intensity but no effect on patient satisfaction overall

Tapentadol (1)

- Class 3 opioid (second line)… ?
- Combined action: more than an opioid!



Sources: Tzschentke et al, 2007; Vanderah, 2007; Pertovaara, 2006; Janssen Pharmaceuticals, Inc.

Tapentadol (2)

- Long acting and short acting formulations
- Many different dosages
- Class 4 reimbursement (CIVARS)
- No specifications on type of pain
- Side effects: be aware for side effects induced by NA release!

Classification of Opioids

Full Agonists

~~Codeine~~
Fentanyl
Sufentanil
Hydrocodon
Meperidine
Methadone
Morphine
Oxycodone
~~Propoxyphene~~

Partial Agonists

- Buprenorphine

Mixed Agonist-Antagonists

Nalbuphine
Butorphanol
Dezocine
Pentazocine
~~*Tilidine (retard)*~~

Neveneffecten van opioiden

- Dysforie, euforie
- Sedatie
- AH depressie
- Nausea, braken
- Miosis
- Sfinter contractie
- Onderdrukken van maag-darm en blaasfunktie
- Jeuk
- Convulsies
- Tolerantie, afhankelijkheid

Opioids

- Full agonists do not antagonise/reverse effects of other agonists given simultaneously

- No "analgesic ceiling" ….. ??????
  - Dosing limited only by side effects

Partial agonists have dose-related ceiling effect

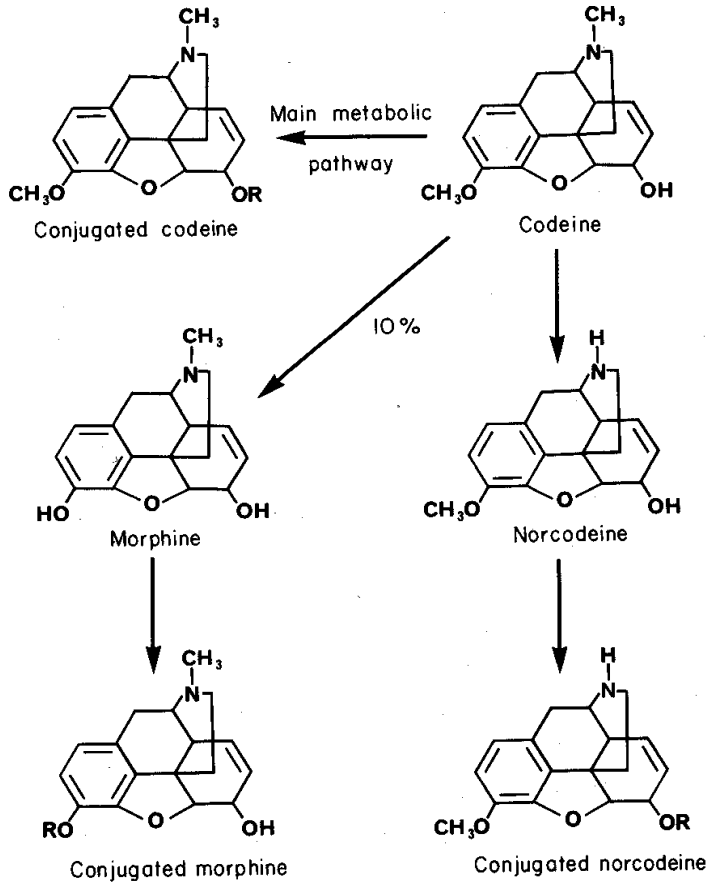
–Less potent analgesics

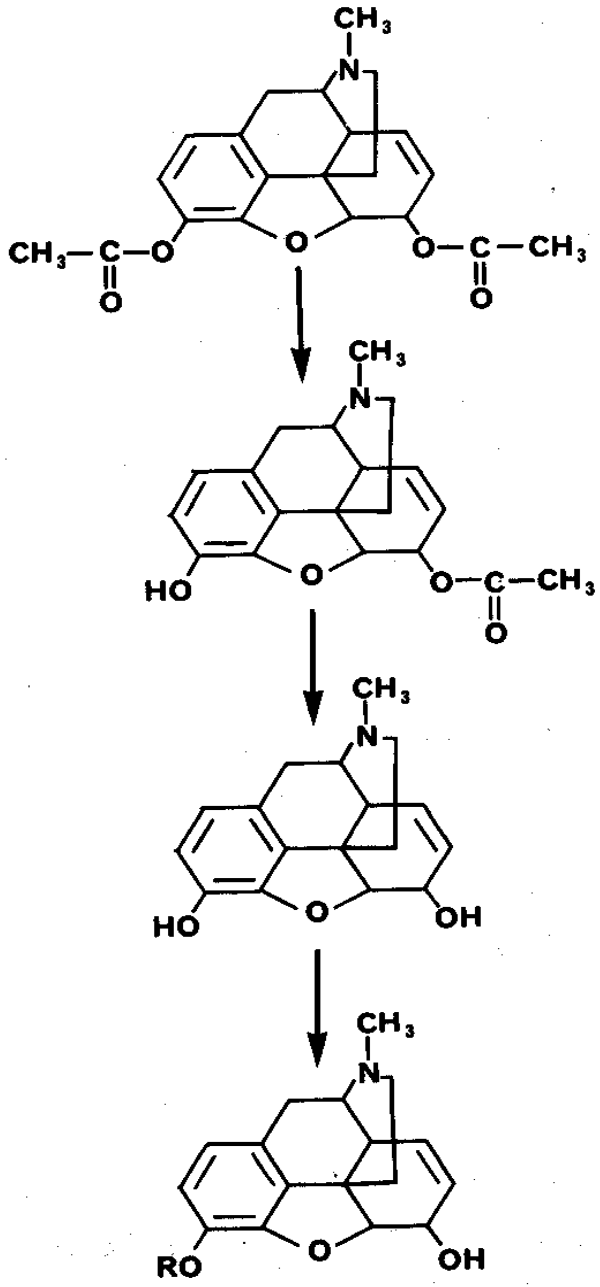
Mixed agonists/antagonists also ceiling effect

–Possibility of withdrawal syndrome

Full agonist : Codeine

- Alkaloid of opium
  - Analgesic effect 5-10x <M+
  - Duration of action: 5 hrs
  - Also anti-tussivum, -diaretic
  - Weak resp. depression
- Associations !
  - With paracetamol
    - Dafalgan codeine, Perdolan
    - Panadol codeine, Lonarid N
  - With aspirin
    - Dolviran
  - Codeine derivates
    - Dihydrocodeine (Codicontin), with longer duration (up to 12 h)





Heroin

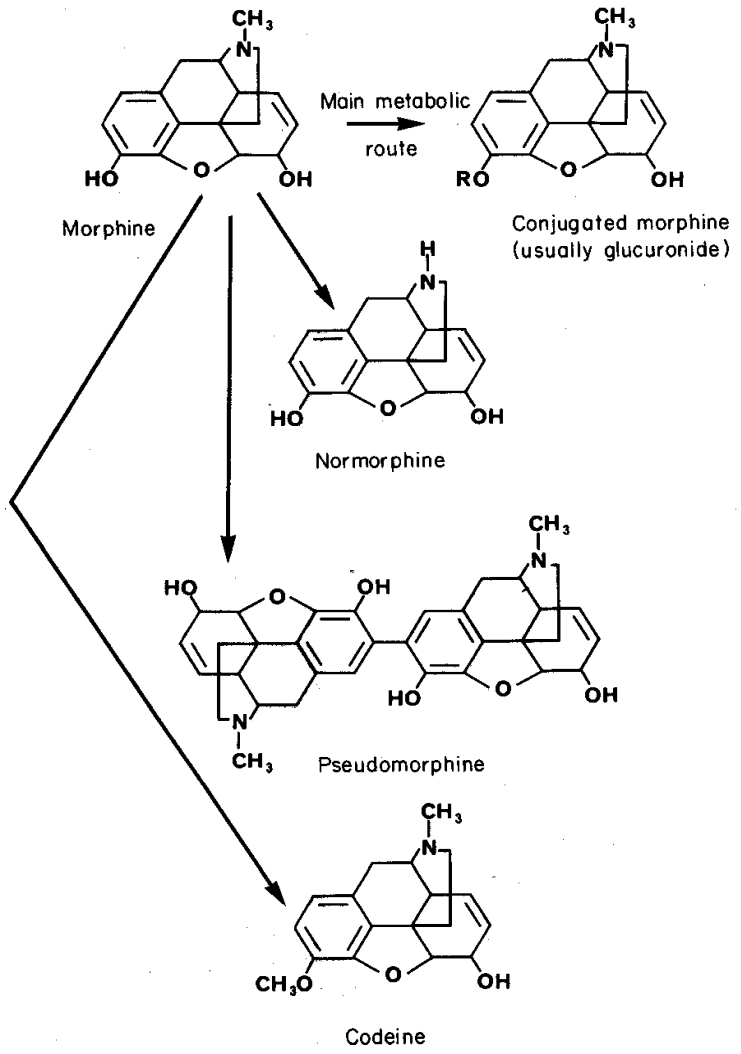
Morphine

Codeine

Full Agonist : Morphine

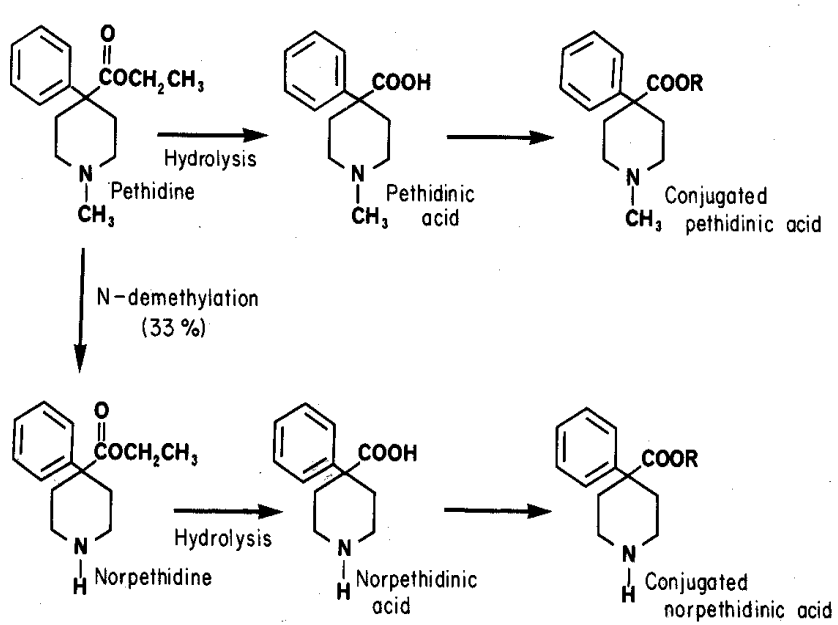
- Principal and….most
- *active* alkaloid of opium
- Many routes (versatile)
- Immediate-release
- Sustained-release
- 25-35% first-pass
- SC / IM: 10 mg / 70 kg
- IV: 2 - 10 mg / 70 kg
- Oral : bioavailability 20%

Parenteral Dose: 5 - 10 mg every 3-6 h



Full Agonist : pethidine

- Pethidine / meperidine (Dolantine®)
  - Weaker analgesic effect than morphine
    - 100mg Dolantine = 10mg Morphine
    - Least potent of synthetic opioids
  - Shorter duration of action than morphine (2 - 4 h)
  - Onset (IM) : 20-30 min
  - *Spasmolytique* activity
  - Side effects:
    - Less respiratory depression
    - CV-depressive action
    - Never during labor



Labor : max fetal concentr after 140 min.
T1/2 : mother 3h, fetus 23h

Full Agonists : Piritramide

- Piritramide (Dipidolor®)
  - Derived from 3,3-difenylpropylamine
  - Less potent than morphine (15-20mg=10mg M+)
  - *Special clinical profile*
    - Less nausea; constipation; resp. depression
    - More sedation
    - Few cardiovascular effects
  - Onset after IM injection: 15 to 20 min
  - Duration: 4 to 6 hours
  - IV ? : 2-4mg/bolus …. (no official indication)

IM: 0.2 - 0.3 mg/kg (20mg) every 6 h (max daily of 80 mg)

Full Agonists : Methadone !

- 100% synthetic substance (L-isomer)
- *High protein binding in tissue*
- Low plasma concentration
  - Low tolerance
  - Longlasting suppression of heroine withdrawal
  - N-demethylation
  - Anti-tussive but
    - actually better substances with
    - Less dependency

Full (synthetic) Agonists

- Fentanyl and Sufentanil
  - More potent than morphine (F50µg = 10mg M+)
  - Sufentanil = Fentanyl x 4-6
  - *Special clinical profile*
    - More sedation
    - Few cardiovascular effects
  - Onset after IV injection: <5min.
  - Duration: 2 to 6 hours
  - Transdermal (Durogesic) as main chronic therapy
  - Effective as breakthrough pain
    - Transmucosal, intranasal, transbucal, ….

Partial Agonist Opioid

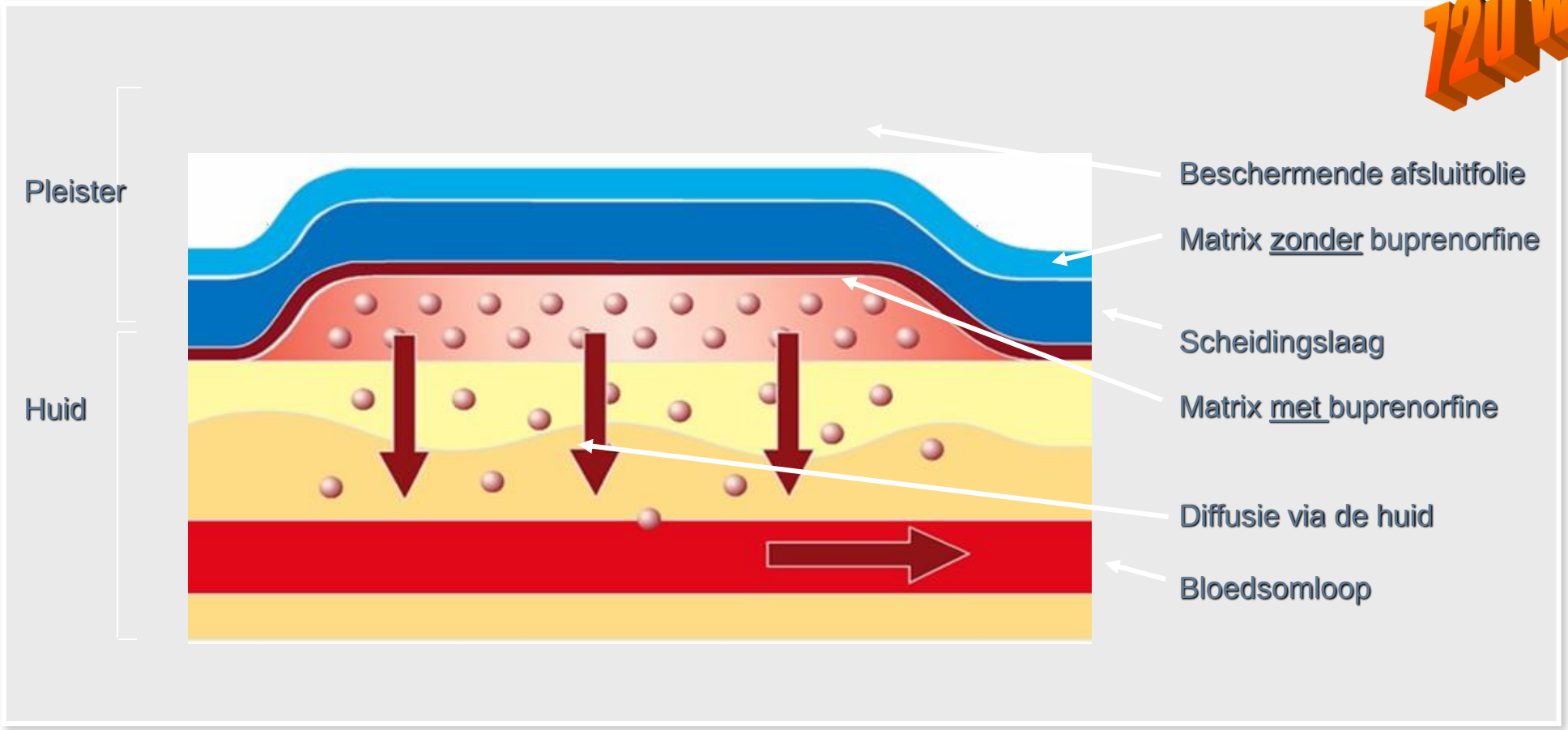
- Buprenorphine (Temgesic®; Transtec®)
  - Semisynthetic derivate of morphine alkaloid thebaine
  - Partial agonist effect at μ-opioid receptor in CNS
    - High affinity at μ-opioid receptors
    - Low intrinsic activity at μ-opioid receptors
    - Relaxation of Oddi Sphinter
  - Sublingual administration:
    - 50% biological availability
    - Peak clinical effect within 1 to 4 hours
    - Elimination half-life between 24 to 37 hours
    - Metabolism in liver (glucuronide conjugation + N-dealkylation)
      - Principally excreted in faeces and urine
  - High lipid solubilty, very high protein binding
    - Remaining in tissues for several days

- *Transdermal*
- 3 different doses
  - 35 µg/h (total dose of 20 mg buprenorphine)
  - 52.5 µg/h (total dose of 30 mg)
  - 70 µg/h (total dose of 40 mg)
- Active during 72 hours
- Matrix technology
  - no leakage ! (1/2 patch possible)
  - No substance abuse possible !

Brand Name		Daily Dose of Buprenorphine	Duration of Use per Patch
TRANSTEC 35 µg/h		0.8 mg	3 days
TRANSTEC 52,5 µg/h		1.2 mg	3 days
TRANSTEC 70 µg/h		1.6 mg	3 days

Matrixsysteem

Grote reserve
12u werking!



Partial Agonist or Ag-Antag ?

- Pentazocine (Fortal®), derivate from Phenazocine
  - Synthetic opioid, too weak antagonistic effect
  - Related to kappa-opioid receptor stimulation
  - Weak antagonist μ-opioid activity
    - Deliberately produced to decrease drug abuse
  - 30 mg (60mg better ?) pentazocine = 10 mg M+
  - Duration of action : 3-6h
  - Metabolised in liver, excreted by the kidneys
  - IV administration increases systemic vascular resistance, and systemic, pulmonary arterial pressure
  - No repeated injections into the skin (fibrosis!)
  - Psychotomimetic reactions
  - Antagonised by nalloxone only.

Agonist + Antagonist (2)

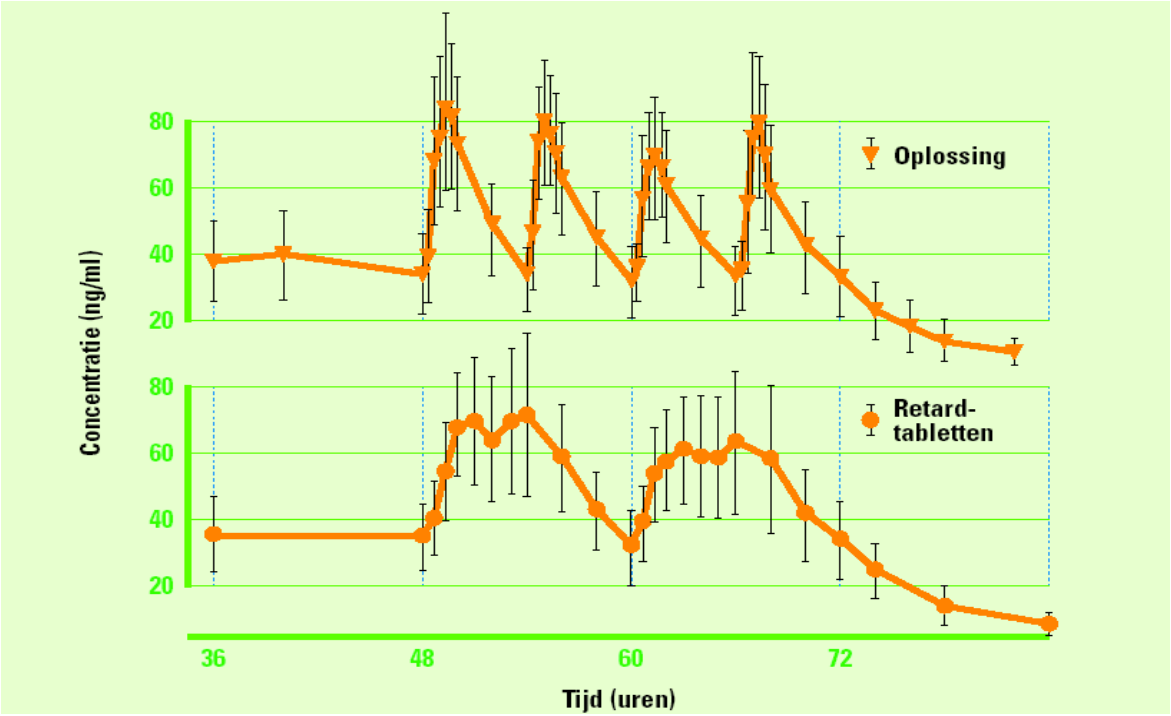
- Tilidine (Valoron) + Naloxone (Valtran®)
  - 100mg = 10mg morphine
  - Analgesic effect 10 - 20 minutes after PO
  - Duration: 4 to 6 hours
  - No cough depression, no cardiovasc. Effects
  - Naloxone < 8mg no clinical effect (analgesia!)
    - First-pass effect of naloxone
  - Overdosage : fear for resp. depression
    - Antagonistic effect proportional to dose

PO Dose: 10 - 20 drops every 6-8 h
Max dose of 4 x 40 drops

Agonist + Antagonist

- Long-acting form (Valtran Retard®)

  Verlengde werking : 12 uren ⇨ 2 x per dag



Agonist + Antagonist (3)

- Oxycodone + Naloxone (Targinact)
  - Idential analgesic effect compared to oxycodone
  - Less gastro-intestinal side effects (obstipation)
    - Scientific evidence very weak
- Many more such combinations to expect in the (near) future, focusing on the obstipation induced by opioids…

Adjuvantia

- **Locale anesthetica**
- **Adrenaline**
- **Clonidine (*postop, labor, chron pijn*)**
- **Ketamine (*postop, postzona*)**
- Neostigmine *(labor)*
- Corticoiden *(chronische pijn, postop)*
- Midazolam *(labor)*
- Magnesium
- Adenosine
- *Baclofen*

Topical analgesic drugs

- Topical lidocaine
  - Reimbursed for PHN
  - Applicable for many peripheral neuropathic pain conditions (localized pain)

- Topical capsaicin
  - Recent peripheral neuropathic pain
  - Long-lasting analgesic effect (3 months)
  - Time consuming application…

Kalinox® + Relivopan® (+ Antafil®)

« Gas and Air »

O_2 N_2O

Oxygen 50 % Nitrous oxide 50%

Klinische effecten

- Zuurstof 50% ter preventie van hypoxie

- Lachgas 50% induceert een toestand van
  - Analgesie (matig)
  - Oppervlakkige sedatie (type 1 – 2)
  - Anxiolytisch effect (soms euforie)
    - Euforie zéker niet altijd aanwezig!
  - Dissociatie en relaxatie
  - Amnesie

Analgesie
voor kortdurende (maximaal 45 minuten)
diagnostische of therapeutische interventies
van minimale tot matige pijnintensiteit
met een maximum van 15 procedures per jaar
bij kinderen ouder dan 3 jaar en volwassenen

(relatieve) Contra-indicaties

- Best NIET te gebruiken in patiënten met
  - Darmobstructie,
  - Pneumothorax,
  - Aandoeningen van middenoor of sinus,
  - Niet gebruiken binnen de 24u na een recente duik,
  - Patiënten met psychiatrische aandoeningen, zoals psychose.

  - Voorzichtigheid geboden tijdens de eerste 2 maanden van de zwangerschap en bij patiënten met verminderd bewustzijn

Toediening – controle door patiënt