Drugs against Pain

- Anesthesia
- Narcotic Analgetics
- Local Anesthetics
- NSAIDs
General Anesthetics

State of drug-induced absence of perception of all sensations: Unconsciousness, analgesia, amnesia and muscle relaxation

General anesthesia is usually induced with intravenous anesthetics, and maintained with inhalation anesthetics

1846 - first surgery under ether-anesthesia; 1847 - introduction of chloroform

Originally, anesthesia was achieved with a single agent (e.g ether, nitrous oxide). However, to satisfy all four anesthesia requirements with one agent necessitates high dosage => increased risk of suppression of vital functions.
General Anesthetics

Inhalation anesthetics:
- Very diverse drugs: ether, nitrous oxide, halogenated hydrocarbons
- Mechanism of action largely unknown (probably inhibition of glutamate receptors and increased activity of GABA receptors)
- Actions are affected by cardiac output and ventilation rate
- Elimination predominantly through exhalation of the unchanged gas

Potency and speed of induction/recovery depend on two properties of the anesthetic:
- **Solubility in blood** (blood:gas partition coefficient)
  - Speed of onset is inversely correlated with the solubility in blood (more soluble => slower onset): blood acts as a reservoir that “needs to be filled”
- **Solubility in lipid** (oil:gas partition coefficient)
  - Determines the potency of the anesthetic
  - **Minimal alveolar concentration** (MAC)
    = alveolar concentration at 1 atm that produces immobility in 50% of the patients exposed to a painful stimulus (usually expressed in Vol%)
    - More lipophilic anesthetics have higher potency
    - Lipophilic anesthetics gradually accumulate in body fat => prolonged “hang-over”
General Anesthetics

Inhalation anesthetics:

• Ether
  – Obsolete (except in underdeveloped regions)
  – Slow onset and recovery
  – Post-operative nausea, vomiting
  – Highly explosive

• Nitrous oxide
  – Low potency (must be combined with other agents)
  – Rapid induction and recovery
  – Good analgesic properties

• Halothane
  – Widely used agent
  – Potent, non-explosive and non-irreant
  – 30% metabolized in liver
    => repeated use can cause liver damage
  – No analgetic properties
  – Causes hypotension (vasodilation, cardio-suppression)
General Anesthetics

Inhalation anesthetics:

- Enflurane
  - Similar to halothane
  - Less metabolized => smaller risk of liver damage

- Isoflurane

- Desflurane

- Sevoflurane
General Anesthetics

Intravenous anesthetics:

- **Thiopental**
  - Barbiturate with very high lipid solubility
  - Rapid action, but accumulates in fat with extended use
  - No analgesic effect
  - Narrow therapeutic range

- **Propofol**
  - Rapidly metabolized => quick recovery
  - Drug of choice for day-case surgery
  - Used as continuous infusion

- **Ketamine**
  - Phencyclidine analogue
  - Good analgesia and amnesia
  - High incidence of hallucinations during recovery

- **Midazolame**
  - Benzodiazepine
General Anesthetics

**Modern anesthesia:**

Employs a combination of drugs to achieve the goals of a “balanced anesthesia”:

- Anxiolytic premedication (Diazepines)
- Autonomic stabilization (Atropin: prevents visceral reflexes)
- Analgetics (Opioids: Fentanyl)
- Muscle relaxant (Pancuronium)
Opioid Analgesics

Opiates:
- Alkaloids derives from *Papaver somniferum*
- Already used 4000 B.C. (*opius* greek: “little juice”)
- 1805: Morphine isolated (*morpheus*: Greek god of dreams)
- 1874: synthesis of heroin (introduced in 1898 by Bayer as a cough medicine)
- Opium tincture heavily used during civil war
- Opiates freely available in the US until 1914
- 1914: Harrison Act
  Prevented physicians from maintaining addiction
Opioid Analgesics

Opiates:
- Act through receptors (7TM, coupled to $G_{\alpha_i}$ or ion-channels) for endogenous opioids: Enkephalins, endorphines,…
- Reduce cAMP, but countereffect: upregulation of adenylate cyclase $\Rightarrow$ tolerance

- Three receptor subtypes:
  - mu ($\mu$): account for most of the morphin effects
  - delta ($\delta$): mediate reduced GI motility and respiratory suppression (in addition to $\mu$)
  - kappa ($\kappa$): mediate dysphoria and contribute to sedation, weak analgesic effect

- Most opioids are full agonists for all receptors
  (exception: Pentazocine, buprenorphine, which are mixed a(nta)gonists based on receptor type)
Opioid Analgesics

Opiates:

Mechanism of analgesic action:

- **Spinal analgesia:**
  Activation of presynaptic opioid receptors => decreased Ca^{++} flux => decreased neurotransmitter (Substance P) release => decreased transmission of pain signal from nocireceptors

- **Supraspinal analgesia:**
  Activation of postsynaptic opioid receptors in the medulla and midbrain => increased K^{+} flux => hyperpolarization => inhibition of neurons in the pain pathway

- Oral opioids are subject to first-pass elimination => low oral bioavailability
- Morphine is metabolized and eliminated via glucuronidation
- Heroin, Fentanyl: very lipophilic => rapid accumulation in the CNS
Opioid Analgesics

Opiates:

Morphine:
- CNS:
  - Sedation and drowsiness
  - Nausea (direct stimulation of the chemoreceptor trigger zone)
  - Cough suppressant (suppressive effect on medulla; independent of analgesic effect)
- Eyes:
  - Pupillary constriction (stimulate parasympathetic portion of the oculomotor nucleus)
- Respiratory system:
  - Strongly suppressive on all phases (frequency; volume)
  - Also depression of hypoxic drive
- GI:
  - Increases resting tone of the smooth muscle of the entire GI tract => segmentation
  - Decreased peristaltic movements, increased sphincter tonus => constipation
- Urinary tract:
  - Increased smooth muscle cell tone => urinary retention

Withdrawal symptoms:
- Mostly autonomic hyperactivity: diarrhea, vomiting, chills, cramps, pain…
Opioid Analgesics

**Codeine** (3-methoxy-morphine):
- Better oral absorption than morphine
- Only 20% of analgesic effect of morphine (does not increase significantly by increasing the dose)
- Prodrug: Converted into morphine by demethylation via CYP2D6 (mutated in ~10% of the population => resistance to the analgesic effect)
- CYP2D6 inhibitors (e.g. Fluoxetine) reduce efficacy of Codeine
- Little euphoria => rarely addictive
- GI and respiratory effects similar to morphine (=> codeine and dihydrocodeine are widely used as antitussiva)

**Dextromethorphan (DXM):**
- Synthetic morphine derivative
- Equally antitussive as codeine
- Does not act through opioid receptors
- No analgesic or GI effects
Opioid Analgesics

Heroin (diamorphine):
- Diacetylated morphine
- Greater lipophilicity => crosses blood/brain barrier better
  => greater “rush”
- Used in UK as analgesic
  (~2x more potent than morphine)

Hydrocodone (Vicodin®):
- Often combined with NSAIDs
- Contained in over 200 preparations in the US

Oxycodone (OxyContin®):
- Used in slow-release formulation to treat chronic pain
- People seeking an alternative to heroin often try OxyContin. They chew the time-release tablets for a quicker high. Some crush the tablet to snort or inject it. Prescriptions are often obtained fraudulently, and in many robberies of pharmacies, only Oxycontin is stolen.
Opioid Analgesics

Meperidine (Pethidine):
- Actions similar to morphine
- Much shorter duration => used during labour

Methadone:
- Actions similar to morphine
- Significantly longer duration ($t_{1/2} = >24$ h) => less psychological dependence
- Used to treat morphine and heroin addiction

Etorphine:
- 1000x more potent than morphine, but similar efficacy
- No clinical advantage
- Used to immobilize wild animals (high potency permits small volumes in darts)

Fentanyl:
- High potency (allows use in transdermal delivery systems)
- Short lasting: used in anesthesia and in patient-controlled infusion systems
Opioid Analgesics

Opiate antagonists:

- **Naloxone:**
  - Short acting
  - Rapidly reversed opioid-induced analgesia and respiratory suppression
  - No effect if no opioids are present
  - Used to treat opiate overdoses and to improve breathing in newborns whose mothers received opioids
  - Induces severe withdrawal symptoms in opioid addicts

- **Naltrexone:**
  - Similar to naloxone, but much longer duration of action
  - Used to “protect” detoxified addicts by preventing any opioid effect if the patient relapses
Local Anesthetics

Mode of action:
- Block generation of action potential by reversibly inhibiting Na\(^{+}\)-influx
- Are weak bases (pK=8-9) => mainly ionized at physiological pH
- Act in their ionized form, but penetrate the cell membrane in the non-ionized form
- Preferentially block activated Na\(^{+}\)-channels = “Use dependence”
  (higher affinity for open/inactivated channel; easier access to open channel)
Local Anesthetics

Mode of action:

- Different nerve fibers show differential sensitivity towards LA:
  - High sensitivity:
    thin, non-myelinated nerve fibers (sensory roots): Pain, touch, temperature
  - Medium sensitivity:
    thin->medium, myelinated nerve fibers (sympathetic nerves): vasomotor, visceromotor function
  - Low sensitivity:
    Thick, myelinated nerve fibers (somatic nervous system): motor function
Local Anesthetics

Classification:

• Aromatic part linked by ester or amide bond to basic side chain:

  - Esters:
    - Inactivated quickly by non-specific esterases in the plasma and tissue
  - Amides:
    - More stable, longer plasma half-lifes
Local Anesthetics

Classification:

- Cocaine
  - First local anesthetic
  - Isolated in 1860 from Coca leaves for their psychotropic effects, knew about the numbing effect they produced on the mouth and tongue)

- Procaine
  - First **synthetic** local anesthetic

- Many more …caines today
## Local Anesthetics

### Clinical use and Administration:

- LA often combined with vasoconstrictors to extend duration of action (also to minimize bleeding)

<table>
<thead>
<tr>
<th>Method</th>
<th>Uses</th>
<th>Drugs</th>
<th>Notes and adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface anaesthesia</td>
<td>Nose, mouth, bronchial tree (usually in spray form), cornea, urinary tract</td>
<td>Lidocaine, tetracaine, (amethocaine) dibucaine, benzocaine</td>
<td>Risk of systemic toxicity when high concentrations and large areas are involved</td>
</tr>
<tr>
<td>Infiltration anaesthesia</td>
<td>Direct injection into tissues to reach nerve branches and terminals</td>
<td>Most</td>
<td>Epinephrine: (adrenaline) or felypressin often added as vasoconstrictors (not with fingers or toes, for fear of causing ischemic tissue damage)</td>
</tr>
<tr>
<td></td>
<td>Used in minor surgery</td>
<td></td>
<td>Only suitable for small areas, otherwise, serious risk of systemic toxicity</td>
</tr>
<tr>
<td>Intravenous regional anaesthesia</td>
<td>LA injected intravenously distal to a pressure cuff to arrest blood flow; remains effective until the circulation is restored</td>
<td>Mostly lidocaine prilocaine</td>
<td>Risk of systemic toxicity when cuff is released prematurely; risk is small if cuff remains inflated for at least 20 minutes</td>
</tr>
<tr>
<td></td>
<td>Used for limb surgery</td>
<td></td>
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<tr>
<td>Nerve-block anaesthesia</td>
<td>LA is injected close to nerve trunks (e.g. brachial plexus, intercostal or dental nerves) to produce a loss of sensation peripherally</td>
<td>Most</td>
<td>Less LA needed than for infiltration anaesthesia</td>
</tr>
<tr>
<td></td>
<td>Used for surgery, dentistry, analgesia</td>
<td></td>
<td>Accurate placement of the needle is important</td>
</tr>
<tr>
<td>Spinal anaesthesia</td>
<td>LA injected into the subarachnoid space (containing CSF) to act on spinal roots and spinal cord</td>
<td>Mainly lidocaine</td>
<td>Onset of anaesthesia may be slow</td>
</tr>
<tr>
<td></td>
<td>Duration of anaesthesia may be increased by addition of vasoconstrictor</td>
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<td>Glucose: sometimes added so that spread of LA can be limited by tilting patient</td>
<td></td>
<td>Main risks are bradycardia and hypotension (owing to sympathetic block), respiratory depression (owing to effects on phrenic nerve or respiratory center); avoided by minimising cranial spread</td>
</tr>
<tr>
<td></td>
<td>Used for surgery to abdomen, pelvis or leg; mainly when general anesthesia cannot be used</td>
<td></td>
<td>Postoperative urinary retention (block of pelvic autonomic outflow) is common</td>
</tr>
<tr>
<td>Epidural anaesthesia</td>
<td>LA injected into epidural space, blocking spinal roots</td>
<td>Mainly lidocaine, bupivacaine</td>
<td>Unwanted effects similar to those of spinal anesthesia but less probable, because longitudinal spread of LA is reduced</td>
</tr>
<tr>
<td></td>
<td>Uses as for spinal anesthesia: also for painless childbirth</td>
<td></td>
<td>Postoperative urinary retention common</td>
</tr>
</tbody>
</table>
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- Act by inhibiting CycloOxygenases (COX) => no PG production
  - COX-1: Constitutively expressed => house-keeping function
  - COX-2: Induced by pro-inflammatory factors (TNFα, IL-1)
  - COX-3: Just recently discovered
- PGs do not cause pain, but sensitize nocireceptors to stimulation (e.g. by 5-HT, Bradykinine, capsaicin, …)
- IL-1 release from activated macrophages (bacteria, etc.) induces COX-2 in the brain => PG E produced => affects thermoregulation => fever => NSAIDs have anti-pyretic effects
- Classical NSAIDs: inhibit both COX-1 and COX-2 (inhibition is reversible, with the exception of Aspirin) => housekeeping PGs reduced => side effects (gastrointestinal, bronchospasms,…)
- 2nd generation NSAIDs: COX-2 specific => only the inflammatory response is inhibited => fewer side effects
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- Aspirin (= Acetyl-Salicylic Acid = ASA)
  - Oldest NSAID
  - Irreversible, non-selective COX inhibitor
    (causes acetylation of COX)
  - Can cause Reye’s Syndrome in children:
    (Combined encephalopacy and liver disorder - 20-40% lethality!!)
    => Avoid Aspirin in children
  - Anti-rheumatic activity requires high doses =>
    CNS effects possible (tinnitus, nausea, etc.) =>
    other NSAIDs have been developed
NSAIDs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- Acetaminophen = Paracetamol (Tylenol®)
  - Most commonly used analgesic/antipyretic
  - Weak anti-inflammatory activity
  - Mechanism still debated (COX-3 inhibitor ??)
  - Overdose can produce fatal hepatotoxicity:
    at high doses (2-3x max. therapeutic dose), a toxic metabolite is produced that is conjugated to glutathione in the liver. If glutathione is depleted, metabolites accumulate => liver necrosis: more than 100 deaths/year in the US!
NSAIDs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- Ibuprofen (Advil®, Motrin®)
- Naproxen (Aleve®)
- Diclofenac (Voltaren®)
- Indomethacine (Indocid®)
NSAIDs

COX-2 specific NSAIDs:

- **Rofecoxib (Vioxx®)**
  - Launched in 1999
  - Marketed in 86 countries: 2.5 bill. /year
  - Recent trial to test Rofecoxib for efficacy in colorectal polyps treatment revealed an increased risk of heart disease (+ 50%) after 18 month continuous use
  - Sept. 2004: Merck *voluntarily* withdrew Vioxx® from the market pending further investigation.

- **Celecoxib (Celebrex®)**
  - April 2005: FDA required Pfizer to include a “boxed warning” indicating a potential risk of cardiovascular side effects

- **Valdecoxib (Bextra®)**
  - April 2005: FDA required Pfizer to withdraw Bextra® from the market due to unfavorable risk vs. benefit profile (mostly already known adverse skin reactions)