Overview

- Pharmacokinetics & pharmacodynamics
- Review of local anaesthetics
- Review of analgesics
- Review of anti-infectives
- Sedative drugs
- Bisphosphonates
- Herbal supplements
- Drug interactions
Pharmacokinetics & Pharmacodynamics
Pharmacokinetics

- What the body does to drugs
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
Pharmacodynamics

* What drugs do to the body
  * Includes duration and magnitude of responses
  * Dose-response considerations
Local Anaesthetics
History of Local Anaesthetics

- Local anaesthetics have been isolated since the 1860s (cocaine)
- Sensory nerve blockade was first described by Halsted in 1884
- “Novocaine” (procaine) was the first commonly used LA in dentistry
- Lidocaine is the original amide LA
  - Commercially available in 1948
  - Articaine is the newest popular LA
    - Released in Canada in 1982 (US in 2000)
Purpose of LA

- To stop the generation and conduction of nerve impulses
- To abort impulses from stimuli, like tooth extraction
  - E.g. To stop the patient from feeling pain
Mechanism of Action

* Local anaesthetics bind to site on Na+ channel
* Inhibits the ↑ permeability to Na+
* Block propagation of action potential
3 common features:

* Lipophilic (aromatic) group
* Intermediate chain with amide or ester linkage
* Hydrophilic (tertiary amine) group
LA Solutions

- By themselves, LA solutions are weakly basic, poorly soluble in water and unstable
- Used as salt solutions (usually HCl) which are water-soluble and stable
  - With the addition of vasopressors, the solutions become acidic
Amide LA’s are primarily biotransformed in the liver
  * Cytochrome P450 CYP3A4

Medical history concerns:
  * Severe liver dysfunction
  * Pseudocholinesterase deficiency (for esters)
Onset determinants

- Proximity to target site
- Concentration
- Lipid solubility
- Nerve morphology
- pH of the tissue
- pKa
* pH at which amount of base = amount of cation
* All LA’s have pKa > 7.4
* ↓ pKa = ↑ potency
# pKa of Local Anaesthetics

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>pK(_a)</th>
<th>% base at pH 7.4</th>
<th>Time to onset (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine</td>
<td>7.6</td>
<td>40</td>
<td>2-4</td>
</tr>
<tr>
<td>Articaine</td>
<td>7.8</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>25</td>
<td>2-4</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.9</td>
<td>25</td>
<td>2-4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>18</td>
<td>5-8</td>
</tr>
<tr>
<td>Procaine</td>
<td>9.1</td>
<td>2</td>
<td>14-18</td>
</tr>
</tbody>
</table>
Henderson-Hasselbalch Equation

\[ pK_a - pH = \log_{10} \frac{\text{Ionized} \quad (BH^+)}{\text{Unionized} \quad (B)} \]
Drug Ionization

Example: Lidocaine

* pKa – pH = log [ionized/un-ionized]
* 7.9 – 7.4 = log [ionized/un-ionized]
* 100.5 = ionized / un-ionized
* ~3 / 1 = ionized / un-ionized
Duration determinants

* Concentration
* Protein binding
* Lipid solubility
* **Redistribution from site**
## Duration of action

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Maxillary Paraperiosteal (min)</th>
<th>IAN Block (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulp</td>
<td>Soft Tissue</td>
</tr>
<tr>
<td>Lidocaine w epi</td>
<td>60</td>
<td>150</td>
</tr>
<tr>
<td>Articaine w epi</td>
<td>60</td>
<td>120-360</td>
</tr>
<tr>
<td>Prilocaine w epi</td>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>Prilocaine plain</td>
<td>15</td>
<td>60-90</td>
</tr>
<tr>
<td>Mepivacaine w levo</td>
<td>50</td>
<td>180-300</td>
</tr>
<tr>
<td>Mepivacaine plain</td>
<td>20</td>
<td>120-180</td>
</tr>
<tr>
<td>Bupivacaine w epi</td>
<td>60</td>
<td>240-540</td>
</tr>
</tbody>
</table>
## LA maximum doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Max (mg/kg)</th>
<th>Max (mg)</th>
<th>Max (mg w/o epi)</th>
<th># cart. (for 70 kg adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lidocaine</td>
<td>7</td>
<td>500</td>
<td>300</td>
<td>13</td>
</tr>
<tr>
<td>articaine</td>
<td>7</td>
<td>500</td>
<td>300</td>
<td>7</td>
</tr>
<tr>
<td>prilocaine</td>
<td>8</td>
<td>600</td>
<td>400</td>
<td>8</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2</td>
<td>200</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>mepivacaine</td>
<td>7</td>
<td>450</td>
<td>300</td>
<td>8</td>
</tr>
</tbody>
</table>
Expressing a % solution in mg/ml
Local Anaesthetic Toxicity

Signs and Symptoms

**Mild**
- Confused
- Talkative
- Slurring
- Muscle twitch
- \( \uparrow \) BP, HR and RR

**Severe**
- Tonic-clonic seizures
- CNS depression
- Drowsiness
- Loss of consciousness
- \( \downarrow \) BP, HR and RR
- CV collapse
Vasoconstrictors

- Epinephrine or levonordefrin are added to LA solutions to increase duration and depth of anaesthesia
  - Use their alpha-agonist interaction with adrenoceptors
  - Short-lasting drugs by themselves
Epinephrine

* rapid onset
* exogenous epinephrine is metabolized by COMT
* short duration of action
  * 5 to 10 minutes if intravenous injection
  * 10 to 20 minutes if intraoral injection
Vasoconstrictors

Epinephrine
1:50,000
1:100,000
1:200,000

Levonordefrin
1:20,000
Trade name = Neocobefrin

1:20,000 = 90 μg per cartridge

Similar concerns to those when using epinephrine

  * Consider the maximum dose of 0.2 mg
Beware of interactions with:

- Non-selective β-blockers
- Tricyclic antidepressants
- Cocaine or amphetamine use
- COMT inhibitors (e.g. Comtan™ for Parkinson’s disease)
  - Not an issue with MAOI
Phentolamine Mesylate (OraVerse™)

- Local anaesthetic reversal agent for adults and children
  - Safe and effective for patients ≥ 6 years and 15 kg
- 2003 report by Rafique et al. (Caries Research, 37: 360-364) noted that 86% of patients receiving LA had moderate dislike of postop numbness
  - 14% report high dislike

www.novalar.com
Phentolamine Mesylate

* A non-selective α-adrenergic antagonist
  * Blocks the effects of vasoconstrictors in LA preparations
  * Increases the redistribution of LA away from injection site
Phentolamine Mesylate

- Reduces duration of anaesthesia by 50%
- Non-toxic and well-tolerated < age 6 years
  - Only observed adverse effect is a minor increase in postoperative pain shortly after return to normal sensation
Phentolamine Mesylate

- Administered via standard dental cartridge in a 1:1 volume dose ratio to local anaesthetic
  - Supplied as 0.4 mg/1.7 mL
  - $13-$17+ per cartridge
- Possible uses:
  - Bilateral mandibular work requiring LA
  - Paediatric patients
  - Mentally challenged patients
Topical Anaesthetics

- Placebo vs. Pharmacology?
- If pharmacology works, then topicals must be placed on dried mucosa for 1-2 minutes
  - NB: Topical anaesthetics are ester LA’s
- Some new research into gels containing KNO₃ and sprays using ethyl chloride
Adverse reactions to LA

Toxicity of LA or vasoconstrictor
Psychogenic reactions
Allergic reactions to LA or to metabisulfite
Methemoglobinemia
Paraesthesia
Adverse reactions

* Psychogenic reactions
  * Syncope is the most common medical emergency
    * Occurs most often at the time of injection
  * Changes in heart rate +/- blood pressure
  * Hyperventilation
  * Nausea and vomiting
Adverse reactions

* Allergic reactions
  * The component ingredients in a cartridge are:
    * Local anaesthetic
    * Vasoconstrictor
    * Metabisulfite
Adverse reactions

* Methemoglobinemia
  * Condition in which cyanosis develops in the absence of cardiac or respiratory abnormalities
  * May be congenital or acquired through drugs or chemicals
  * MetHb is normally <1%
  * Cyanosis and respiratory distress may occur with MetHb >10%
Methemoglobinemia

* Associated with prilocaine (or severe benzocaine) overdose
* Prilocaine’s metabolite o-toluidine can block MetHb reductase, leading to $\uparrow$ MetHb
* Appears 3 - 4 hours after administration
Methemoglobinemia
- Unresponsive to O$_2$
- Pulse oximeter readings are abnormal (~85%)
- Blood is chocolate brown
- Treated by 1% methylene blue IV
- Avoid prilocaine or benzocaine if congenital methemoglobinemia
Paraesthesia
Paraesthesias

* There are numerous reports regarding the association between 4% solutions and a higher-than-expected incidence of paraesthesias
  * Note the risk:benefit equation
    * Overall paraesthesia incidence is 1:800,000 injections
  * There has been an RCDSO advisory regarding 4% solutions used for blocks
Paraesthesia

- Broad term for prolonged anaesthesia or altered sensation, beyond expected duration of action of local anaesthetic
Paraesthesia

- Most are transient, usually resolving within 8 weeks
  - If not, prognosis is very poor
- Precise cause not known with certainty
  - Hemorrhage into nerve sheath
  - Scar formation
  - Alcohol or sterilizing solution
  - Neurotoxicity - controversial
Adverse reactions

* A 21-YEAR RETROSPECTIVE STUDY OF REPORTS OF PARESTHESIA FOLLOWING LOCAL ANESTHETIC ADMINISTRATION
  * Haas and Lennon, JCDA, 1995, 61:319-330
The overall incidence of paraesthesia following local anesthetic administration for non-surgical procedures in dentistry is very low → 1:785,000

If, however, paresthesia does occur, the results suggest that it is more likely if either articaine or prilocaine is used

Reasons are speculative only
Results (1973-1993)

Articaine | Bupivacaine | Lidocaine | Mepivacaine | Prilocaine

0 10 20 30 40 50 60

Articaine > Prilocaine

Bupivacaine

Lidocaine

Mepivacaine
Sites of Paraesthesia

1973-1993
* Tongue = 64.3%
* Lip = 29.4%
* Lip & Tongue = 6.3%

1994-1998
* Tongue = 70%
* Lip = 20%
* Chin = 9%
* Cheek = 9%
* Other = 14%
Adverse reactions

* **Nerve injury caused by mandibular block analgesia**
  * Prospective study in Denmark
  * Results: Neurologic evidence of neurotoxicity, not mechanical injury
  * Articaine had > 20-fold ↑ in paraesthesia compared to all other locals combined
Practice Alert: Paraesthesia Following Local Anaesthetic Injection

“Until more research is done, it is the College’s view that prudent practitioners may wish to consider the scientific literature before determining whether to use 4% local anaesthetic solutions for mandibular block injections.”
**Adverse reactions**

* Retrospective Review of Voluntary Reports of Non-Surgical Paresthesia in Dentistry
  * Gaffen and Haas, 2009, Journal of the Canadian Dental Association, 75(8): 579

**OBJECTIVES:**
* To analyze cases of paresthesia associated with local anesthetic injection that were reported to the province of Ontario’s Professional Liability Program (PLP) from 1999 to 2008 inclusive
* To update previous study (1995)
Results

Sites:
* Tongue: 79.1%
* Chin/lower lip: 28.0%
* Tongue and lower lip together: 9.9%
* Cheek 4.4%

Symptoms:
* Altered taste: 14.3%
* Pain on injection: 19.2%
* Dysesthesia: 9.9%
Results: Percentage of paresthesia
Occurrence of paresthesia after dental local anesthetic administration in the United States

Gabriella A. Garisto, DDS; Andrew S. Gaffen, DDS; Herenia P. Lawrence, DDS, MSc, PhD; Howard C. Tenenbaum, DDS, PhD; Daniel A. Haas, DDS, PhD
Figure 3. Expected versus observed frequency distribution per local anesthetic drug from November 1997 through August 2008.
Conclusions

- Incidence is very low
- Yet data are strongly suggestive of an association
- No proof of cause-effect
- It is not the drug *per se*
- Higher concentrations may simply predispose to greater effect
Analgesics
General guidelines

* Eliminate the source of pain
* Consider adjusting regimens according to the patient’s needs and response
* Maximize NSAID/acetaminophen doses before adding opioids
* Patients who do not respond to one NSAID may respond to another
* Avoid chronic use
Arachidonic Acid Cascade

- Lipoxygenase
  - Leukotrienes
    - Bronchospasm
    - Inflammation

- COX-1
  - PG's
    - GI protection
    - Uterine cont.
    - Renal function

- COX-2
  - TXA's
  - Platelets
  - PG's
    - Pain
    - Inflammation
## Analgesic Efficacy
(Oxford League Table)

<table>
<thead>
<tr>
<th>Analgesic (mg)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac (20)</td>
<td>1.8</td>
</tr>
<tr>
<td>Diclofenac (100)</td>
<td>1.9</td>
</tr>
<tr>
<td>Acetaminophen (1000) + codeine (60)</td>
<td>2.2</td>
</tr>
<tr>
<td>Diclofenac (50)</td>
<td>2.3</td>
</tr>
<tr>
<td>Naproxen (440)</td>
<td>2.3</td>
</tr>
<tr>
<td>Ibuprofen (400)</td>
<td>2.4</td>
</tr>
<tr>
<td>Ketorolac (10)</td>
<td>2.6</td>
</tr>
<tr>
<td>Ibuprofen (200)</td>
<td>2.7</td>
</tr>
<tr>
<td>Morphine (10 IM)</td>
<td>2.9</td>
</tr>
<tr>
<td>Acetaminophen (1000)</td>
<td>3.8</td>
</tr>
<tr>
<td>ASA (650)</td>
<td>4.4</td>
</tr>
<tr>
<td>Codeine (60)</td>
<td>16.7</td>
</tr>
</tbody>
</table>
Non-steroidal anti-inflammatory agents are central to pain control in dentistry
- They inhibit COX-2 +/- COX-1 enzymes
  - Tissue damage activates COX-2
NSAID Therapeutic Effects

* Analgesic
* Anti-inflammatory
* Anti-pyretic
* Anti-dysmenorrheal
# NSAID* Dosages for Post-Op Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose (mg)</th>
<th>Frequency</th>
<th>Daily Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>325-1000</td>
<td>q 4-6 h</td>
<td>4,000</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400</td>
<td>q 4-6 h</td>
<td>2,400</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>1000, then 500</td>
<td>q 12 h</td>
<td>1,500</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500, then 250</td>
<td>q 6-8 h</td>
<td>1,375</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>10</td>
<td>q 4-6 h</td>
<td>40 (5 days)</td>
</tr>
</tbody>
</table>
Ibuprofen

- An effective and popular NSAID
- Analgesic, anti-inflammatory and antipyretic
- Effective doses are 200 mg – 400 mg q 4-6 h
  - Maximum daily dose = 1200 mg
  - Loading doses are effective
- Solubilized liquigels and ibuprofen lysine have faster onset and better peak analgesia than conventional tablets
Vioxx® and Celebrex® are the famous examples

The benefits should be:

- Less GI bleeding
- Fewer gastroduodenal ulcers

Is there a predisposition to myocardial infarction?

- Vioxx® voluntarily withdrawn from the market in 2004
• Dosage is 200 mg bid
• Equal efficacy to 650 mg ASA in dental pain studies
• Less effective than ibuprofen or naproxen
NSAID Adverse Effects

- Increased bleeding*
- Gastric mucosal damage
- Dyspepsia
- Renotoxicity
- Anaphylactoid reactions
NSAID contraindications

* Gastric ulcers
* Bleeding dyscrasias or concerns
* Significant renal disease
* asa (or other NSAID) hypersensitivity
* Combination of severe asthma, nasal polyps and multiple allergies
  * Can lead to ARDS
NSAID contraindications

* Pregnancy
  * Especially in the 3\textsuperscript{rd} trimester
* Children
  * asa only
* Elderly
* Concurrent use of certain other drugs
NSAID strategies

* Consider:
  * Pre-operative dosing
  * Loading doses
  * 4-hour interval instead of prn for the first day
Acetaminophen

- Analgesic of choice in dentistry
- Effective analgesic and anti-pyretic
  - No NSAID side effects
  - Not anti-inflammatory
- Very safe at normal doses
  - Hepatotoxic at high doses
- Mechanism of action not entirely clear
**Dosages**

- Adult dose is 500-1,000 mg q 4-6 h to a maximum of 4 grams per day
- Paediatric dose is 10-15 mg/kg q 4-6 h to a maximum of 80 mg/kg
Two different mechanisms of action for analgesia

- Potentially synergistic in the short-term
  - Potentially renotoxic in the long-term
Opioids

- Usually used for analgesia for moderate to severe pain in dentistry
- Other opioid effects:
  - Sedation
  - Mood alteration
  - Antitussive
  - Respiratory depression
  - Nausea and vomiting
  - Constipation
Mechanism of action

- Analgesia site of action is the CNS
- Possible peripheral anti-inflammatory action
  - One study compared supplemental PDL injections with fentanyl vs. mepivacaine with epi
**Opioids**

* Equipotent doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral dose (mg)</th>
<th>IM dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>120</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
<td>75</td>
</tr>
</tbody>
</table>
Recommended oral doses

- Codeine = 60 mg
- Oxycodone = 5-10 mg
- Meperidine = 100 mg
They have the advantage of convenience

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acetaminophen (mg)</th>
<th>Codeine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol #1</td>
<td>300</td>
<td>8</td>
</tr>
<tr>
<td>Tylenol #2</td>
<td>300</td>
<td>15</td>
</tr>
<tr>
<td>Tylenol #3</td>
<td>300</td>
<td>30</td>
</tr>
<tr>
<td>Tylenol #4</td>
<td>300</td>
<td>60</td>
</tr>
</tbody>
</table>
Opioids

* Addiction is a real possibility
* The public (and the government) are currently on high alert about the use of opioids in healthcare
Analgesic Tips

* Maximize NSAID (or acetaminophen) before adding opioid
* Optimize dosing regimen before switching
* If the patient does not respond to one NSAID, they may respond to another
* Consider pre-operative or loading doses
Mild to moderate pain

Acetaminophen (up to 1000 mg)

NSAID

Add codeine to NSAID or acetaminophen

Add oxycodone with acetaminophen

Add codeine or oxycodone
Prescribing Principles

* Use only when there is an indication
* Choose the narrowest spectrum drug that will be effective
* Consider the risk/benefit equation
* Prescribe an adequate dose
  * Adequate frequency
  * Adequate duration
Reasons for Failure

- Wrong drug or dose
- Bacterial resistance
- Host defences depressed
- Poor compliance
Antibiotic Actions

**Bactericidal**
- Penicillins
- Metronidazole
- Cephalosporins
- Aminoglycosides*
- Vancomycin*

**Bacteriostatic**
- Clindamycin
- Erythromycin
- Tetracyclines
* Oral penicillins are penicillin V and amoxicillin
* Pen V is narrow-spectrum against gram-positive Strep and others
  * Drug of choice for orofacial infections
  * Dose = 300-600 mg q6h
* Amoxicillin is broad-spectrum and better absorbed orally
  * Dose = 250-500 mg q8h
Penicillins

* Adverse reactions
  * Allergy
  * Diarrhea
  * Nausea and vomiting
  * Pseudomembranous colitis
  * Candidiasis
Penicillins

- Allergy rate is 1-10% of the population
- Penicillins responsible for 75% of anaphylaxis deaths
  - 400-800 deaths per year in the US
- Mild anaphylaxis occurs 1:200 courses
- Severe anaphylaxis occurs 1:2,000 courses
Clindamycin

- An alternative for penicillin-allergic or penicillin-resistant patients
- Active against gram-positive and gram-negative anaerobes and facultative/aerobic bacteria
- Dose = 150-300 mg q6h
Pseudomembranous colitis

- Also known as antibiotic-associated diarrhea (AAD)
- Broad-spectrum antibiotic use alters the composition of gut bacteria
  - This allows the overgrowth of other bacteria
  - *Clostridium difficile (C. difficile)* is the beneficiary of interest here
    - The presence of *C. difficile* and its toxins cause pseudomembranous colitis
    - Characterized by diarrhea, fever and abdominal pain
Risk factors

Drugs include:
- Penicillins (esp. ampicillin)
- Cephalosporins
- Clindamycin
- Erythromycin

Advanced age
Females with genitourinary disease
Uremic patients (e.g. kidney dialysis patients)
Pseudomembranous colitis

- Treatment
  - Stop all antibiotics
  - Keep the patient hydrated
  - Refer to a physician
  - Prescribe:
    - Vancomycin 500 mg po qid for 2 days (if severe)
    - Vancomycin 125 mg po qid for 10-14 days
    - Metronidazole 500 mg po tid for 7-14 days
    - Metronidazole IV
    - Probiotic therapy (*Saccharomyces boulardii*) has been tried adjunctively
Macrolides

- Group includes erythromycin, clarithromycin and azithromycin
- Erythromycin was the former drug of choice for penicillin-allergic/penicillin-resistant patients
  - Numerous GI adverse effects
- Active against gram-positive aerobic/facultative staph and strep and gram-negative anaerobes
Trade name is Flagyl™
Active against obligate, gram-negative anaerobes only
Used in combination with penicillin
Avoid concurrent use of alcohol or warfarin
Dose = 250-500 mg tid
Tetracyclines

- Group includes tetracycline, doxycycline (Vibramycin, Periostat) and minocycline (Minocin)
  - Broad-spectrum, bacteriostatic
- Useful in treatment of periodontal disease
- Widespread resistance
- Host of adverse effects including: tooth staining, photosensitivity, blood dyscrasias, GI effects
Antibiotic Adverse Reactions

* From Resnick and Misch (2008):
  * Overall incidence is 6-7%
  * Possible reactions include:
    * GI tract complications
    * Colonization of resistant or fungal strains
    * Cross reactions with other medications
    * Pseudomembranous colitis
    * Development of resistant bacteria and superinfection
      * Little concern about short-term use
Antibiotic Prophylaxis
Antibiotic Prophylaxis

- Indicated for patients with:
  - Prosthetic heart valves
  - History of infective endocarditis
  - Cardiac transplant with subsequent heart valve problem
  - Some congenital heart conditions
    - Unrepaired cyanotic disease (incl. shunts and conduits)
    - Repaired defect (<6 months) with prosthetic material or device
    - Repaired defect with residual defect at or adjacent to the site of repair
Coverage is **not** indicated for patients with:

- Surgically constructed systemic pulmonary shunts
- Isolated secundum atrial septal defect
- Previous coronary artery bypass graft surgery
- Physiologic (functional, innocent) heart murmurs
- Pacemakers and implanted defibrillators
Antibiotic Prophylaxis

* Indicated for the following procedures:
  * Implant placement
  * Extractions
  * Periodontal procedures
  * Reimplantation of avulsed teeth
  * Endodontics beyond the apex of the tooth
  * Intraligamentary injections
  * Subgingival placement of fibres or strips
  * Placement of orthodontic bands
  * Polishing of teeth or implants where bleeding is expected
### Antibiotic Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose</th>
<th>Paedo Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2 g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600 mg po/IV</td>
<td>20 mg/kg po/IV</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g IM/IV</td>
<td>50 mg/kg IM/IV</td>
</tr>
</tbody>
</table>
Patients already taking an antibiotic used for prophylaxis should:

* Be prescribed an antibiotic from a different class
* Be scheduled at least 9 days after the completion of the current prescription
Total Joint Prosthesis

- May be indicated for patients at increased risk including:
  - < 2 years post-surgery
  - Inflammatory joint disease
  - Immunosuppression (incl. drug-induced, radiation-induced, HIV)
  - Previous joint infections
  - Type I diabetes mellitus
Prophylaxis for Total Joint Prostheses

- Prophylaxis may be indicated for patients at increased risk including:
  - < 2 years post-surgery
  - Inflammatory joint disease (e.g. rheumatoid arthritis, lupus)
  - Immunosuppression (incl. drug-induced, radiation-induced, HIV)
  - Previous joint infections
  - Type I diabetes mellitus
  - Hemophilia
  - Malignancy
- *The literature is unclear*
Total Joint Prostheses

* Regimens:
  * Amoxicillin or cephalexin 2 g po, 1 hour pre-op
  * Clindamycin 600 mg po/IV, 1 hour pre-op
CYP3A4 is a major metabolizing enzyme

- Part of the cytochrome P450 enzyme system
- Clarithromycin, erythromycin and the azole antifungals (e.g. ketoconazole, fluconazole) are potent inhibitors of CYP3A4
  - Single-dose regimens, as in antibiotic prophylaxis are not of major concern
Antibiotics and Oral Contraceptives

- Anecdotally reported
- Scientific evidence implies rifampin (Rifadin®, Rofact™) only
- Virtually untestable
  - Rationale is that antibiotics reduce enterohepatic recycling of estrogen → subtherapeutic blood levels that allow ovulation
The concept of using antibiotics to enhance the outcome of implant surgery is not new

- Adel et al. (1981) used Penicillin V for 10 days
- Adel (1985) used 2 g Penicillin V for 10 days
- Buser et al. (1990) used short-term amoxicillin or erythromycin
Cochrane Review by Esposito et al. (2008) investigated the use of antibiotics to prevent complications in implants.

- Two randomized controlled studies were subjected to meta-analysis.
- Showed a statistically significant higher number of implant failures in the group that did not receive antibiotics.

“It might be recommendable to suggest the use of one dose of prophylactic antibiotics prior to dental implant placement:

- 2 g of amoxicillin preoperatively?
Sinus lift pre-/perioperative medication

- Clavulin® = amoxicillin and clavulanic acid
  - Dose = 875/125 mg bid for 7 days
- Chlorhexidine 0.12% rinse
- Start both medications 1 day pre-operatively
Possible complications that may require medications are:

- Site infection
  - Chlorhexidine 0.12% mouthrinse bid for 2 weeks
- Nasal congestion
  - Pseudoephedrine (Sudafed®) 120 mg q12h
    - Phenylephrine (Sudafed PE®) 10 mg q4h
  - Oxymetazoline 0.05% (Claritin® Nasal Pump, Drixoral®) 2 sprays in each nostril q12h
    - Afrin® in the US
    - NB: other formulations of Claritin® are loratidine, an antihistamine
Bisphosphonates
Bisphosphonates

- They inhibit bone resorption by inhibiting osteoclasts and impairing angiogenesis
- Indicated in the treatment of:
  - Osteoporosis
  - Paget’s Disease
  - Prolonged glucocorticoid therapy
  - Metastatic cancers (e.g. breast, lung, prostate and renal)
  - Osseous lesions associated with multiple myeloma
Bisphosphonates

- Associated with osteonecrosis of the jaws
  - Other bones rarely affected
- Oral vs. intravenous
  - Consider as 2 distinct risk groups
- Oral formulations include alendronate (Fosamax™), risedronate (Actonel™), ibandronate (Boniva™) and etidronate (Didrocal™)
Osteonecrosis Incidence

- Bisphosphonate-associated osteonecrosis (BON) incidence estimates:
  - ~0.8%-20% of patients in cancer therapy
  - 0.01%-0.04% of patients taking oral formulations
    - 0.09%-0.34% in cases of dental extractions
  - 30 million prescriptions in the US in 2006
  - < 10% of BON cases associated with oral bisphosphonates

Ref.: ADA, JADA 139(12): 1674-1677, 2008
**ADA Recommendations**

* General dentistry
  * Areas of bony infection should be treated immediately
  * No change in routine care

* Periodontal disease
  * Try to use non-surgical therapies with re-evaluation in 4-6 weeks
  * Use bone grafting and guided tissue regeneration judiciously
* Oral and maxillofacial surgery
  * Discuss risks (though small) and alternate treatments (e.g. RCT, FPD’s, RPD’s)
  * Post-operative prophylactic antibiotic use should be for risk of infection vs. use of bisphosphonates

* Implants
  * Placement of implants may pose increased risk
  * Peri-implantitis should be approached non-surgically first
Sedative Agents
Spectrum of Anaesthesia

- Conscious Sedation
  (minimal and moderate*)
  - Deep Sedation
  - General Anaesthesia
Conscious Sedation

Definition

* “… a minimally to moderately depressed level of consciousness that retains the patient’s ability to... maintain an airway and respond appropriately to physical stimulation and verbal command.”

* Ref: RCDSO, 2008
Deep Sedation

Definition

* “… a controlled state of depressed consciousness, accompanied by partial loss of protective reflexes, including inability to respond purposefully to verbal command.”

* Ref.: RCDSO, 2008
General Anaesthesia
Definition

* “... a controlled state of unconsciousness accompanied by partial or complete loss of protective reflexes including inability to maintain an airway independently ...”

* Ref.: RCDSO, 2008
Warning:

Any method of sedation and any choice of drug can lead to any level of consciousness.
Useful Conscious Sedation Drugs

Nitrous Oxide
Benzodiazepines
Antihistamines*
Nitrous Oxide and Oxygen

* The Good:
  * Fast onset, fast offset
  * Easy to administer
  * No lasting effects
    * 0.004% metabolized
  * Very safe
Nitrous Oxide and Oxygen

* The Bad:
  * Difficult for claustrophobic patients
  * May not be strong enough
  * Requires active dentist participation
Oral Medications

* **The Good:**
  * Familiar, noninvasive route of administration
  * No special office equipment is needed*

* **The Bad:**
  * Not titratable or recoverable
    * Benzodiazepines are reversible but not orally
    * Beware of DOCS* protocols
  * Slow onset
  * Patients must be accompanied home

Ref.: Donaldson et al., Anesthesia Progress, 54:118, 2007
Benzodiazepines

- An anxiolytic-specific category of drugs
- Act on GABA_A receptors in the CNS to hyperpolarize cells
  - Lowers brain activity
- Little effect on the respiratory and central nervous systems
Benzodiazepines

- Effects are sedation, anterograde amnesia and anxiolysis
- Popular choices are midazolam, triazolam, diazepam and lorazepam
  - Peak of action in about 1 hour, except for midazolam
  - Be careful with multiple doses or alternate routes of administration (e.g. sublingual)
Non-BZD GABA Agonists

* Agents include:
  * Zolpidem (Ambien)
    * Fast onset, short duration, no active metabolites
  * Zopiclone (Imovane)
    * Similar pharmacologic profile to zolpidem
  * Ramelteon (Rozerem)
    * A melatonin receptor agonist
Sedation is a side effect

Agents include hydroxyzine (Atarax), diphenhydramine (Benadryl) and promethazine (Phenergan)

Very safe
Warning:
Oversedation = medical emergency
Drug Therapy in the Elderly
Factors to consider

- Pharmacokinetic changes
- Pharmacodynamic changes
- Systemic disease
- Polypharmacy
Pharmacodynamics

* CNS drugs have magnified effects (e.g. benzodiazepines)
* Can result in
  * Excessive sedation
  * Mental confusion
  * Delirium
  * Respiratory depression
Some examples of diseases that affect pharmacologic effects include:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>↑ serum half-life and concentration</td>
</tr>
<tr>
<td>Congestive heart disease</td>
<td>↑ serum half-life and concentration</td>
</tr>
<tr>
<td>Benign prostatic hypertrophy</td>
<td>↑ urinary retention with anticholinergics</td>
</tr>
<tr>
<td>Dementia</td>
<td>↓ ability to comply with prescriptions</td>
</tr>
</tbody>
</table>
Use of prescription medications, OTC medications, natural medicines and alternative medicines is very widespread in Canada

- Concerns for adverse drug reactions and drug interactions
- According to a 2009 report from Ramage-Morin (Statistics Canada)
  - In 2005, pharmacists dispensed an average of 35 prescriptions per person aged 60 to 79
    - 74 prescriptions per person aged 80 or older
    - Compared with an overall average of 14 prescriptions per Canadian
- Math, co-morbidities and physiologic changes put seniors at risk
53.1% of institutionalized seniors and 12.8% of seniors in private households reported polypharmacy (taking 5 medications or more in the past 2 days).

97% of institutionalized seniors reported taking some medication in the past 2 days.

76% of seniors living in private households.
Specific considerations

* Local anaesthetics
  * No change in administration
  * Consider reducing maximum dose if the patient has congestive heart disease
  * Limit vasoconstrictor dose to 40 μg per appointment
Specific considerations

* Acetaminophen
  * Analgesic of choice
  * Dosage of 325-1000 mg q4h to a daily maximum of 4 g
  * Reduce the daily maximum if there is alcoholism or significant liver disease
Specific considerations

* NSAIDs
  * Note the possibilities for bleeding, ulceration or perforation
  * Increased risk of GI toxicity
  * Increased risk of renal toxicity
  * Increased risk of hepatic toxicity
  * Consider celecoxib (Celebrex®) as your NSAID
Specific considerations

* Opioids
  * Level of effect increased
  * Duration of effect prolonged
  * Increased likelihood of adverse reactions
  * Consider using a reduced dose or avoid opioids
Specific considerations

- Antibiotics
  - Increased risk of pseudomembranous colitis
  - No need to alter regimens solely because of age
Nitrous oxide & oxygen
  * First choice for conscious sedation
  * Advantages
    * Titratability
    * Rapid onset and offset
  * Disadvantages
    * Patient acceptance
    * Limited effectiveness
    * Equipment costs
    * Not useful for Alzheimer’s/dementia patients
Specific considerations

- Oral sedation
  - Advantages
    - Easy to administer
    - No equipment costs*
  - Disadvantages
    - Dosage is a guess
    - Onset is delayed and unreliable
    - Effects are prolonged
    - Limited efficacy
    - Many side effects
    - May not be suitable/effective for dementia patients
Pharmacotherapy for the elderly patient

* Goals
  * Review the patient’s current drug list
  * Simplify the treatment regimens
  * Reduce the number of drugs and the dosing frequency
  * Monitor the patient after providing a prescription
Herbal Supplements
A survey by *Prevention Magazine* in 2000 suggested that 33% of American adults used herbal supplements.

70% of the consumers may not tell their healthcare providers about this.

Government oversight is not as strict as with conventional drugs.

2013 study at U of Guelph showed that one-third of the products did not contain what they said they did.

**Suggested reading:** *Do You Believe In Magic* by Paul Offitt
## Antiplatelets

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>CV problems, antimicrobial, cold/flu, diabetes</td>
</tr>
<tr>
<td>Ginger</td>
<td>Motion sickness, sore throat, indigestion</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>CV disorders, memory loss</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Physical weakness, immune depression</td>
</tr>
<tr>
<td>Willow</td>
<td>Pain, flu, rheumatism</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Pain, muscle spasm, gynecological complaints</td>
</tr>
</tbody>
</table>
## Anticoagulants

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse chestnut</td>
<td>Varicose veins, hemorrhoids</td>
</tr>
<tr>
<td>Red clover</td>
<td>Skin conditions, cough</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Diabetes, GI disorders, inflammation</td>
</tr>
</tbody>
</table>
## CNS Depressants

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kava</td>
<td>Insomnia, stress, mild pain</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Muscle spasm, sedative, wound healing</td>
</tr>
<tr>
<td>Valerian</td>
<td>Insomnia, muscle cramps, rheumatic pains, restlessness</td>
</tr>
</tbody>
</table>
St. John’s wort

- Popular supplement used for depression, anxiety, and insomnia
- May interact with the CYP-450 enzyme system, which may increase metabolism and excretion of benzodiazepines
Ephedra

* Also known as Ma-huang
* Used for weight reduction, energy enhancement, and asthma treatment
* Produces increased sympathomimetic activity
  * Contains ephedrine and pseudoephedrine
* May reduce effectiveness of anxiolytics, sedatives, anaesthetics, and other CNS depressants
Drug Interactions
There is a decreased antihypertensive effect with ACE inhibitors, diuretics and β-blockers.

- The production of some renal vasodilatory prostaglandins are dependent on active COX-1 and COX-2 enzymes.
  - ASA is the exception.
- OK when co-prescribed for a short term (5 days or less).
All non-specific NSAID drugs are highly protein-bound (99%) and interfere with clotting.

Warfarin is highly protein-bound (99%) and has a low therapeutic index.
- An increase to 3% circulating warfarin can be significant
- Same with methotrexate

The same increase in effect is true for NSAIDs and oral hypoglycemics (e.g. glyburide).
- The result is hypoglycemia
NSAIDs and SSRIs

* SSRIs (e.g. fluoxetine [Prozac], paroxetine [Paxil], sertraline [Zoloft]) can interfere with platelet aggregation
  * Increased risk of upper GI bleeding
NSAIDs and Acetaminophen

- May be synergistic in the short-term
- Can cause renal damage over time
- This holds true NSAID combinations also
Lithium toxicity may result, but the evidence is not clear

Avoid this combination, especially in the elderly
Toxicity to methotrexate may result

- Low-dose methotrexate (e.g. for arthritis) is OK
- High-dose methotrexate (e.g. for cancer) should be avoided
Cocaine is a vasoconstricting stimulant that works by blocking the reuptake of the neurotransmitter norepinephrine

- This stimulates the myocardium and the CNS
- Administering epinephrine can result in seizures, stroke, cardiac dysrhythmias or myocardial ischemia
Opioids and Alcohol

* While the mechanisms of action with these drugs is distinct, they both affect the CNS
  * Can get additive sedative effects
This a metabolic issue with the cytochrome P450 system

- P450 CYP3A4 is the most abundant of these enzymes
  - Affects midazolam, triazolam and diazepam
  - Inhibited by grapefruit juice, erythromycin and clarithromycin and the azole antifungals (e.g. ketoconazole)
- Leads to a greater effect and longer duration
Other interactions

- Metronidazole and alcohol
- Acetaminophen and alcohol
- Bactericidal and bacteriostatic antibiotics
- NSAIDs and cardioprotective doses of ASA
- Antibiotics and oral contraceptives
Adverse Events During Paediatric Dental Anaesthesia

* Article by Chicka et al. in *Pediatric Dentistry*, 2012; 34: 231-238
  * Analyzed 17 closed malpractice insurance claims in the US from 1993-2007
    * 1 GA, 3 LA, 13 sedation & LA
    * 9 outcomes of “major” severity (i.e. death or brain damage)
    * 8 outcomes of “minor” severity (i.e. no permanent morbidity)
Adverse Events During Paediatric Dental Anaesthesia

- Article by Chicka et al. in *Pediatric Dentistry*, 2012; 34: 231-238
- 82% of the claims involved children < 6 years
  - Most sedated children are < 6 years (78%)
- Average age of “major” outcomes = 3.6 years
  - There is an inverse relationship between patient age and sedation risk
- 47% of the outcomes were “minor”
  - Good management vs. self-limiting events
Adverse Events During Paediatric Dental Anaesthesia

- Article by Chicka et al. in *Pediatric Dentistry*, 2012; **34**: 231-238
  - No single sedative agent was most frequently associated with “major” outcomes
    - Drug dose more important than drug choice
  - 41% of the claims involved an overdose of LA
    - LA toxicity may be masked by concomitant BZD use
  - Most claims involved events at the dental office
    - The dentist is likely to be the first responder
      - Important for the dentist and the team to be ready