Pharmacology for the Dental Practitioner: an Overview

Crown and Bridge Study Club
April 12, 2019

Dr. Aviv Ouanounou, BSc, MSc, DDS, FICO, FICD
Assistant Professor, Clinical Sciences - Pharmacology –
Faculty of Dentistry, University of Toronto - Toronto ON - Canada
Outline of this presentation:

- Introduction
- Local anaesthetics
- Analgesics in dentistry
- Anti-infectives
- Special topics in dental pharmacology
- Drug therapy during Pregnancy and lactation
- Geriatric pharmacology
Introduction
Pharmacology (from pharmakon, the Greek word for drug) is the study of drugs (substances that produce changes in the body).
Pharmacokinetics

What the body does to the drugs
Absorption, distribution, metabolism, excretion

Pharmacodynamics

What drugs do to the body.
Basic Principals

1. Never administer or prescribe a drug without an indication (does the pt needs the drug?) (e.g. antibiotics for the prevention of infective endocarditis).

2. Balance the risks and benefits of administering or prescribing any drug.

3. Proceed only if the balance is favorable.

4. Drugs not a magic bullet, they are always associated with ADRs and DIs.
Being able to give drugs is not a right-- it’s a privilege in dentistry
LOCAL ANAESTHETIC
LOCAL ANAESTHETIC

- Local anesthetics are the most frequently used pharmaceutical agents in clinical dentistry.
- Approx. 300 million cartridges of local anesthetic are used annually by dentists in the US (Malamed 1997).
- Average Canadian dentist administer over 1800 cartridges of local anesthetic per year (Haas and Lennon, 1995).
Local Anesthetics...

- Are drugs used to prevent or relieve pain in specific regions of the body without loss of consciousness.
- Reversibly block pain sensation by blocking nerve conduction.
Excitation of a nerve segment leads to an increase in permeability of the cell membrane to Na+ ions. The rapid influx of Na+ ions to the interior of the nerve cell causes depolarization and this is needed to initiate an action potential (impulse).
Nerve Conduction Physiology

Handbook of Local Anesthesia, 5th edition
Malamed
Nerve Conduction Physiology

Na+ Channel Transition Stages

Handbook of Local Anesthesia, 5th edition
Malamed
Nerve Conduction Physiology

Summary

- At rest: Na+ Channels are closed
- At depolarization: Na+ Channels open
- At repolarization: Na+ Channels inactivated (nerve is refractory to stimulus)
- At recovery: Na+ Channels convert from inactivated to resting state (nerve regain the ability to conduct an action potential)
Mechanism of action of LA:

LA produce a conduction block of neural impulses, preventing the passage of Na+ through Na+ channels.
-Sodium influx through these channels is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve.

-When a nerve loses depolarization and capacity to propagate an impulse, the individual loses sensation in the area supplied by the nerve.
The Na+ channel acts as a receptor for local anesthetic molecules.

The action of LA is dependent on the conformational state of the Na+ channel.

LA binds more readily to the Na+ channel during depolarization (when it is open).

LA prevents permeability to Na+ thus slowing the rate of depolarization.
Sodium influx through these channels is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve.

When a nerve loses depolarization and capacity to propagate an impulse, the individual loses sensation in the area supplied by the nerve.
Mechanism of Action:

1. Blockade of the Na+ channel
2. Decrease in Na+ conductance
3. Depression of the rate of depolarization
4. No threshold achieved
5. No AP
ONSET OF ACTION

- Dose
- Lipid Solubility
- Site of Injection
- Nerve Morphology
- PH of the tissue
- Pka of the drug
ONSET OF ACTION

Pka

- Relative concentration of the non ionized lipid-soluble form and the ionized water-soluble form, as expressed by the pKa
ONSET OF ACTION

Henderson-Hasselbalch Equation

\[ p\text{Ka} - \text{pH} = \log \left[ \frac{\text{ionized}}{\text{un-ionized}} \right] \]

- This equation describes the derivation of pH as a measure of acidity (using pKa, the negative log of the acid dissociation constant) in biological and chemical systems.
• Unionized form = can penetrate the cell membrane = EFFECTIVE

• Ionized form = Can NOT penetrate the cell membrane = NOT EFFECTIVE
The pKa of most LA is in the range of 8.0-9.0
ONSET OF ACTION

Pka of Amides Local anesthetic:

- Lidocaine-7.9
- Articaine- 7.8
- Prilocaine- 7.9
- Mepivacaine- 7.6
ONSET OF ACTION

Pka of Ester Local Anesthetic:

- Procaine- 8.9
- Chloroprocaine-9.0
- Tetracaine- 8.2
ONSET OF ACTION

- LA with a pKa closest to physiological pH will have a higher concentration of non ionized base that can pass through the nerve cell membrane, and generally a more rapid onset
ONSET OF ACTION

EXAMPLES:

- Lidocaine vs. Procaine
ONSET OF ACTION

Lidocaine

- Has pKa of 7.9
- At physiological pH (7.4), it exists in a ratio of 3:1 ionized to unionized
ONSET OF ACTION

Procaine

- Has pKa of 8.9
- At physiological pH (7.4), it exists in a ratio of 32:1 ionized to unionized
ONSET OF ACTION

• Since Lidocaine has a greater proportion of the unionized form than Procaine, it will have faster onset of action.
ONSET OF ACTION

- What happens when LA are injected to a site of infection?
ONSET OF ACTION

● Lidocaine

- Has pKa of 7.9

- Site of infection pH (5.9), ratio of 1000:1 ionized to unionized

- A very low fraction of unionized local anesthetic is available for diffusion into the cell
The molecule of LA consists of 3 structural parts:

1. Lipophilic Center (aromatic group)
2. Hydrophilic Center (tertiary amine)
3. Intermediate Group (amide or ester)
Handbook of Local Anesthesia, 5th edition

Malamed
STRUCTURE

Amides LA:

- Lidocaine
- Mepivacaine
- Prilocaine
- Bupivacaine
- Articaine
Esters LA:

- Proacine
- Chloroproacaine
- Tetracaine
- Benzocaine
- Cocaine
## STRUCTURE

<table>
<thead>
<tr>
<th>Aromatic residue</th>
<th>Intermediate chain</th>
<th>Amino terminus</th>
<th>Aromatic residue</th>
<th>Intermediate chain</th>
<th>Amino terminus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td></td>
<td></td>
<td>Iodocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxycaine</td>
<td></td>
<td></td>
<td>Etidocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine</td>
<td></td>
<td></td>
<td>Mepivacaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td>Bupivacaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td></td>
<td></td>
<td>Prilocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td></td>
<td></td>
<td>Articaine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dydrogesterone is a ketone.*

*Handbook of Local Anesthesia, 5th edition Malamed*
DURATION OF ACTION

- Reversal agent
- Phentolamine mesylate
- Was approved by the FDA May 2008
- Formulation use in dentistry (reduces duration of anesthesia recovery by half)
- Used to limit the duration of soft tissue anesthesia
DURATION OF ACTION

Its primary action is vasodilation due to alpha blockade
Has been shown to accelerate the reversal of the lingering soft-tissue numbness associated with the widely used anesthetic-vasoconstrictor combinations

Mandibular block: 60 mins faster
Maxillary injection: 45 mins faster
Administered via standard dental cartridge (1.7 mL)
Expensive ($15 per cartridge)

Possible uses:
- Bilateral mandibular work requiring LA
- Paedo patients
- Mentally challenged patients
ADVERSE REACTIONS TO LOCAL ANAESTHETICS
Adverse reactions

- Psychogenic
- Allergic
- Toxicity
- Paresthesia
Adverse Reactions

Psychogenic

- Hyperventilation
- N & V
- Syncope
- Increase in HR and/or BP
- Decrease in HR and/or BP
- Intravascular administration of a vasoconstrictor
Adverse Reactions

Allergic Reactions

- Rarely occur
- Usually an ester derivative of p-aminobenzoic acid is involved
- Methylparaben
- Epinephrine (non existing)
Adverse Reactions

Toxicity

- Very rare
- Usually due excessive doses or Intravascular injection
- Other factors (e.g. site, speed of injection, presence or absence of vasoconstrictor)
Adverse Reactions

Toxicity

- CNS toxicity
- CVS toxicity
Adverse Reactions

Toxicity

- Very rare
- *Usually due excessive doses or Intravascular injection*
- Other factors (e.g. site, speed of injection, presence or absence of vasoconstrictor)
MAXIMUM DOSES

- **LA Max Dose**
- Articaine---- 7mg/kg
- Bupivacaine---- 2mg/kg
- Lidocaine----7 mg/kg
- Mepivacaine----6.5 mg/kg
- Prilocaine---- 8 mg/kg
General Concepts for calculating the max dose of LA

- % solutions represent grams/100 ml
- Move the decimal place to the right
- e.g. 2% lidocaine = 20 mg/ml
- Each cartridge contains 1.8 ml
MAXIMUM DOSES

Lidocaine for 25 kg child

- Max dose is 7 mg/kg
- 7mg/kg X 25 kg = 175 mg
- 2% lidocaine = 20 mg/ml
- 175mg / 20 mg/ml = 8.75 ml
- 8.75 ml / 1.8 ml (in each cartridge) = 4.86
PARESTHESIA

- Potential complication of LA administration
- Characterized by persistent anesthesia or altered sensation ranging from complete numbness to burning, tingling or continual pain
- Usually transient and resolve within 6-8 weeks
- Cause: Unknown
- Possible factors
PARESTHESIA

Haas DA, Lennon D.


- Analyzed 143 cases reported to the Royal College of Dental Surgeons of Ontario (RCDSO) over a 21-year period.

- The results from their analysis seemed to indicate that 4% local anesthetics had a higher incidence of causing paresthesia, after the injection.
The authors concluded that the overall incidence of Paresthesia following local anesthetic administration for non-surgical procedures in dentistry in Ontario is very low, with only 14 cases being reported out of an estimated 11,000,000 injections in 1993.

However if paresthesia does occur, the results of this study are consistent with the suggestion that it is significantly more likely to do so if either articaine or prilocaine is used.”
PARESTHESIA

JADA July 2010

• “Occurrence of Paraesthesia After Dental Local Anesthetic Administration in the United States”
  • By:
    • Gabriella A. Garisto, DDS,
    • Andrew S. Gaffen, DDS,
    • Herenia P. Lawrence, DDS, MS, PhD,
    • Howard C. Tenenbaum, DDS, PhD and
    • Daniel A. Haas, DDS, PhD
Paraesthesia arising from a local anesthetic injection alone is a rare event.

- 4% anesthetic solutions, namely prilocaine and articaine, are more highly associated with the development of paraesthesia than are those of lower concentration.

- Dentists should consider these results when assessing the risks and benefits of using 4 percent local anesthetics for mandibular block anesthesia.
PARESTHESIA

What to do?

RCDSO
PARESTHESIA

PRACTICE ALERT

“Paraesthesia Following Local Anaesthetic Injection”

Dispatch Magazine, Summer 2005
Vol 19, no.3
PARESTHESIA

Risk Management Advise

“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 anesthetic solutions for mandibular block injections”
1. Hematomas
2. Trismus
3. Broken Needles
Hematomas are formed by the leakage of blood from vessels into the surrounding tissue.

The larger the vessel the more rapidly and dramatically the development of a hematoma will occur.

Most likely site of a hematoma is after PSA (posterior superior alveolar) nerve blocks.

This is due to the proximity to the # of veins and arteries of the injection target site.

IA (inferior alveolar) nerve blocks have the 2nd highest rate of hematoma formation.
- Although rare, after a hematoma develops there is a chance of trismus and infection.
- Hematomas while healing are marked by a very noticeable discoloration of the face.
- The majority heal with no complication and require no further Tx.
Tx of Hematoma

• Rapid recognition and response can alter its clinical course.
• Be alert to hematoma formation.
• Size is limited to the amount that the tissue will stretch while blood is emptying into it.
• **APPLY PRESSURE AND ICE.**
• Respond to initial signs of swelling
• Discontinue treatment for the day
Instruct the patient to:
1. Apply ice intermittently for the next 6 hours (15 mins. on/ 15 mins. off)
2. Avoid ASA or Non-steroidal anti-inflammatory.

Advise the patient:
1. Regarding development of bruising and discolorations
2. To notify you immediately of any changes
3. Signs and symptoms of infection
4. Limited jaw opening
Trismus is defined as a motor disturbance of the trigeminal nerve.

- Inability to open the mouth
- Can be caused by many factors (tetanus, tumors, fractures, ankylosis)
- Consequence of dental anesthesia - cause is hemorrhage and muscle trauma.
- Relatively common due to trauma caused by needle movements
- Most frequently affects the medial pterygoid muscle.
Trismus-Tx

- Apply hot, moist towels approximately 20 minutes every hour (5 minutes on, 10 minutes off)
- Use analgesics as required
- Open and close the mouth gradually/repeatedly
• Monitor for signs of infection (Increasing heat, redness, elevated temperatures, and pain)
• May require antibiotics
• Signs and symptoms fail to improve or worsen (Refer to an oral surgeon)
BROKEN NEEDLES
RISK FACTORS:

- Unexpected movements
- Factors increasing risk:
  1. Smaller diameter needles and needles in deeper penetrations
  2. Bending needles at the hub
  3. Needle penetrations to the hub
- Inspect needles before use.
- Avoid inserting needles to the hub.
- Choose the appropriate needle gauge and length
- Use long needles for deeper penetrations.
Avoid excessive forces on needles (i.e., repositioning).
Avoid excessive numbers of penetrations with the same needle.
Avoid bending at the hub (i.e., PDL injections).
MANAGEMENT

- Keep a sterile haemostat or forceps nearby.
- Do not allow the patient to close if there is breakage.
- If the needle is visible, remove it with a haemostat.
What if the needle is not visible?

1. Inform the patient
2. Immediately refer to an oral/maxillofacial surgeon
3. Keep accurate records (Location, Needle size, any unforeseen events, patient communication)
Vasoconstrictors
What happens if we won’t have epi in our LA?

- An increased rate of absorption of the LA into CVS
- Increased risk of LA toxicity, as a result of higher plasma levels of LA
- Decreased duration of action of the LA, because it diffuses away from the injection site more rapidly
- Increased bleeding in the area of LA administration
Vasoconstrictors are drugs that constrict blood vessels to oppose the dilatory actions of the LA.
VASOCONSTRICTORS

- Decrease the blood flow to the site of injection
- Decrease the risk of toxicity
- Increase the duration of LA
- Decrease bleeding at the site of administration
Epinephrine Interactions

- Beta blockers
- Tricycle Antidepressants
- GA
- Cocaine and Amphetamines
VASOCONSTRICTORS

Drug Interactions

- Medical Hx
- Pre-op BP and HR
- Minimize epinephrine administration
- Monitor BP and HR
- When concern: DO NOT USE 1:50,000 epi
Analgesics
Third Molar Removal Model
EVIDENCE FROM CLINICAL TRIALS
Acetaminophen
NSAIDs
Opioids
NSAIDs
ARACHIDONIC ACID

Lipoxygenase
Leukotrienes

Epoxygenase
Epoxides

COX-1,2

Reactive O₂ species
Isoprostanes

PGG₂
PGH₂

PGD synthase
PGF synthase
PGE synthase
PGI synthase
Tx synthase

PGD₂
PGF₂
PGE₂
PGI₂
TxA₂
ARACHIDONIC ACID CASCADE

- Prostaglandins and Thromboxane
  - Gastric protection
  - Uterine contraction
  - Renal function
  - Platelet aggregation

- TISSUE DAMAGE
  - Prostaglandins
    - Pain
    - Inflammation
    - Renal function

COX-1

NSAIDs Block

COX-2
ADR with NSAIDs

- Increased bleeding
- Dyspepsia
- Gastric mucosal damage
- Renal impairment
- Can be associated with allergy
NSAID CONTRAINDICATIONS

- Gastric ulcers
- Bleeding concerns
- ASA or other NSAID-induced hypersensitivity
NSAID CONTRAINDICATIONS

- Significant renal disease
- Late in pregnancy
- Children (ASA)
- Elderly (reduce dose/frequency)
- Concurrent use of specific drugs
NSAIDs Interactions:

1. CVS meds: ACE inhibitors, diuretics, beta blockers, digoxin
2. CNS meds: e.g. Lithium, SSRI
3. Anti-coagulants
4. Methotrexate
5. Acetaminophen
6. Other NSAIDs
7. More...
NSAIDS + ANTIHYPERTENSIVES

- Diminished effect with:
  - angiotensin converting enzyme inhibitors (ACE inhibitors)
  - diuretics
  - beta-blockers
NSAIDS + ANTIHYPERTENSIVES

- Rx NSAID if need for < 5-6 days
- Avoid NSAID in severe congestive heart disease
- Monitor BP if concern
Toxicity may result, yet evidence is not clear
Avoid combination or Rx for the very short-term
Avoid in elderly
NSAIDS + ANTICOAGULANTS

Recommendations

- Gastrointestinal bleeding may result
- Avoid combination when possible
- High dose ASA (> 3 g/day) is most severe
NSAIDS + METHOTREXATE

Recommendations

- Toxicity may result
- Avoid combination if high-dose methotrexate, as used for cancer therapy
- Low-dose methotrexate, as used for arthritis is of little concern
NSAIDS + SSRI

- Reports of ↑ bleeding
- SSRI have antiplatelet effects
- Likely not an issue in short-term Rx
Misoprostol

- Beneficial Drug interaction with NSAIDS
- Cytotec
- PG analog
- To prevent gastric bleeding
- Absolute contraindication during pregnancy
Misoprostol

- Beneficial Drug interaction with NSAIDS
- Cytotec
- PG analog
- To prevent gastric bleeding
- Absolute contraindication during pregnancy
 NSAID PRESCRIBING

- Loading dose
- Consider pre-op dose
- Consider round-the-clock dosing for the first 24 hours if severe pain
- Maximize non-opioid before adding an opioid
Ibuprofen

Adult dose:
- 400 - 600 mg
- Every 6 hours
- Daily max: 2400 mg
- Trade name examples:
  - Advil, Motrin
Flurbiprofen

**Adult dose:**
- 50 - 100 mg
- Every 4 - 6 hours
- Daily maximum: 300 mg
Diflunisal

**Adult dose:**
- 1,000 mg stat, then 500 mg
- Every 12 hours
- Daily max: 1.5 grams
Naproxen

Adult dose:
- 500/550 mg stat, then 250/275 mg
- Every 6 - 8 hours
- Daily max: 1,375 mg
- Trade name examples:
  - Naprosyn, Naproxen, Aleve
Why were COX-2 inhibitors developed?

- In the U.S. alone, reports that over 16,000 patients die every year from GI bleeds following NSAID use.
COX-1

- Constitutive
- The “Good one”
- responsible for normal functions such as:
  - maintenance of GI integrity
  - initiate platelet aggregation
  - regulate renal blood flow
The “Bad one” induced in inflammation contributes to:
- pain
- edema
- tissue destruction

may also play a role in kidney and brain
COX-2 INHIBITORS
COX-2 INHIBITORS
COX-2 INHIBITORS
Where should the benefit be?

- Less gastroduodenal ulcers
- Less GI bleeding
COX-2 INHIBITORS

Adverse effects:

- Assume same adverse actions on kidney as with non-selective NSAIDs
Adverse effects:

- Evidence of predisposition to MI
- Pro-thrombotic effect due to an imbalance between thromboxane and prostacyclin
Celecoxib

- First COX-2 inhibitor released
- Celebrex®
- Availability
  - 100 and 200 mg tablets
- Dosage:
  - 200 mg daily for rheumatoid arthritis
  - 200 - 400 mg daily for osteoarthritis
  - 200 mg BID for pain
Celecoxib restrictions

- Do not use if pt has had MI, CVA, angina, CHF
- Do not use if pt has risk factors for MI or CVA
- Rx for lowest dose and shortest time
- Only use for certain conditions:
  - Acute pain from surgery or tooth extraction qualifies
NSAIDs and CVS Disease

- Recent data now challenge safety of all NSAIDs if risk factors for MI/CVA exist
- Controversial
  - Circulation 2007;115:1634-1642
  - Circulation 2011;123:2226-2235
  - BMJ 2011:342:c7086
- Naproxen may be safest for these pts
- Ibuprofen appears fine if < 1 week
- Keep Rx of any NSAID as short as possible
Rofecoxib (Vioxx)

- in dental pain studies rofecoxib 50 mg had equal efficacy compared with ibuprofen 400 mg
- withdrawn in Sept 2004 because of CVS concerns with long-term use
- FDA review in Feb 2005
Other COX-2 Inhibitors

- **Valdecoxib (Bextra)**
  - Sales suspended in 2005

- **Parecoxib**
  - Pro-drug converted to valdecoxib
  - Injectable
  - Not yet available

- **Etoricoxib**
  - Available outside of North America
COX-2 Inhibitors

What are the benefits?

1. Less GI Bleed
2. Less GI Ulcers
• Celebrex® is the first COX-2 inhibitor released.

• Dosage:
  • 200 mg BID for dental pain

**DO NOT USE if pt has:**

**MI, angina, CHF or if pt has risk factors for MI**
ACETAMINOPHEN
Acetaminophen

- Analgesic
- anti-pyretic
- No GI effects or bleeding issues as with NSAIDs
- adult dose: 325 mg q4h prn pain
- Peado: 10-15 mg/kg q4h to a max of 65 mg/kg
- Now maximum of 1.5 grams/day (Health Canada lowered recommended maximum because of pts taking additional acetaminophen in other formulations)
- high doses may damage liver
- DIs???
Metabolism of Acetaminophen

Hersh and Moore, 2004
Hepatic conjugation: glucuronidation (40-70%) and sulfation (20-40%)
CYP450-mediated N-acetylation to highly reactive metabolite NAPQI (10-16%)
Most common cause of drug-induced acute liver failure
In North America acetaminophen liver toxicity accounts for over 35,000 hospitalizations and 650 deaths every year.
OPIOIDS
Opioids

- Mod-severe pain
- MOA: CNS—Opioids receptors (mu, kappa and delta).

**Other effects:**
- Sedation
- Antitussive
- Respiratory depression
- N & V
- Constipation
Opioids

- Nausea, vomiting
- Constipation
- Respiratory depression
- Hypotension
- Acute urine retention
- Tolerance and physical dependence
OPIOIDS

Definitions:

1. Dependence
2. Tolerance
3. Abuse
4. Addiction
Physical Dependence:

- Pt needs this for the normal hemostasis
- The development of withdrawal symptoms once the drug is stopped
Withdrawal Symptoms of Heroin:
- Increased pain
- Agitation
- Poor sleep
- Increased BP
- Sweaty
- N & V
- Increased urination
- Diarrhea
- Watery eyes, running nose, yawning
- Shivering and sweating
- Abdominal cramps and muscle aches
- Involuntary leg movements
- Diarrhea; an increased sensitivity to pain
- Difficulty in sleeping
- These intensify over the next several days and then start to diminish
Tolerance:

- Administration of the same dose has less effect
- The decline in potency of a drug experienced with continued use, so that higher doses are needed to achieve the same effect.
- Due to PK
- Enzyme induction
- PD (less receptors, signal transduction is reduced)
Drug Abuse:

1. Harmful use of a drug
   - To user
   - To society
2. Inappropriate use of a drug for nonmedical purpose
3. If sustained can lead to physical and behavioral dependence
# Opioids for dental pain

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>DOSE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine</td>
<td>60 mg q4h</td>
</tr>
<tr>
<td>oxycodone</td>
<td>5 – 10 mg q4h</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>2 – 4 mg q4h</td>
</tr>
</tbody>
</table>
Codeine

**Adult dose:**
- 60 mg
- Every 4 - 6 hours
- With a non-opioid
Codeine

- Weak Agonist
- Metabolized to morphine
- 2D6
- Genetic variability (of how much 2D6 enzyme you have)
Codeine in a pt who is an ultra rapid metabolizer of 2D6

Excessive Morphine
Combinations

Acetaminophen or ASA with:

- codeine (8, 15, 30, 60)
- oxycodone (2.5, 5)
Oxycodone

Adult dose:
- 5 - 10 mg
- Every 4 - 6 hours
- Combined with ASA or acetaminophen
- Trade names:
  - Percodan, Percocet
## Combinations

<table>
<thead>
<tr>
<th></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>
The problem with these are the dependency and addiction that may develop over time.
How do people get these drugs?

- Diversion of the drugs
- Over Prescribing
- Under Prescribing
- Clinical Judgment
Diversion of Prescription Drugs & Drug-Seeking Behavior
(How do people get these drugs?)
- Thefts and break-ins from pharmacies and warehouses
- Customers in drugstore parking lots
- Breaking into homes of patients who use pain medications
- Employees stealing from hospitals
- Inappropriate prescribing by health professionals
- Providers selling drugs
- Patients with legitimate prescriptions selling the pills
- Drug shoppers
• Easy target for drug seeking
• Next to family physicians, DDS (tied with internal medicine) are next most likely to Rx opioids
• “Double-doctoring”
• Theft of Rx pads
Prescribe Cautiously!!!
General principles for the management of acute pain in dentistry
1. Eliminate the source of the pain
2. Individualize analgesic regimens
3. BEFORE Rx Opioids: is diversion of prescribed opioids a concern?
4. Maximize the non-opioid before adding an opioid (ibuprofen 600mg, acetaminophen 1,000mg)
5. For NSAIDs consider: loading dose OR pre-op dose OR QID instead of prn for days 1 – 3.
6. If the pain is estimated to be moderate-to-severe:
   - Consider using bupivacaine to gain long duration of local anaesthesia
   - Consider: increasing the NSAIDS OR recommend acetaminophen with codeine.

7. If the pain is estimated to be severe-very severe consider using oxycodone with acetaminophen (such as Percocet).

ANTI INFECTIVES
Special topics in Dental Pharmacology
• Pregnancy and Lactation
• Geriatric pharmacology
Pregnancy and Lactation
Drug therapy during pregnancy: implications for dental practice

A. Ouannounou* and D. A. Haas²

VERIFIABLE CPD PAPER

*Assistant Professor, Department of Clinical Sciences (Pharmacology), Faculty of Dentistry, University of Toronto; Professor, Dean and The Joseph Zweigenberg Dental Chair, Faculty of Dentistry, Department of Pharmacology, Faculty of Medicine, University of Toronto.

*Correspondence to: Dr. Ali Ouannounou Email: aou.ouannounou@dentistry.utoronto.ca

Accepted 22 February 2015
DOI: 10.1056/ijd.2015.299

British Dental Journal 2015: 220: 410-417

This PEAK article is a special membership service from RGOSO. The goal of PEAK (Practice Enhancement and Knowledge) is to provide Ontario dentists with key articles on a wide range of clinical and non-clinical topics from dental literature around the world.

PLEASE KEEP FOR FUTURE REFERENCE.

Supplement to 2017 Vol. 31, No. 1 issue of Dispatch magazine
In pregnancy drug treatment presents a special concern due to the threat of potential teratogenic effects of drug and changes in the physiology.
Drug Use In Pregnancy

1991 WHO International Survey of Drug Utilization in Pregnancy:

- 86% of women took medication during pregnancy
- Average of 2.9 Rx
• Many women take medications in the early weeks of pregnancy before realizing that they are pregnant
• Many pregnant women take OTC medications
• Many women use social drugs such as tobacco or alcohol or illicit drugs
While avoiding medications during pregnancy is desirable, it is often not possible.

- May be dangerous (mom with asthma, epilepsy, HBP)
- During pregnancy new medical conditions may be develop and old ones may be exacerbated requiring pharmacological intervention
- Failure to manage these conditions may harm the mother and/or the fetus
Physiological Changes During pregnancy:

CVS
Respiratory System
GI system
Renal System
Haematological system
Dental and Oral changes
Pharmacokinetics During Pregnancy
Drug Absorption

• High circulating progesterone slow the gastric emptying as well as small intestine motility
• Not significant clinically
Drug Distribution

- Pregnancy is accompanied by an increase in Total Body Water
- Increase in Plasma volume
- Decrease in plasma albumin
- This may increase the free drug fraction and thus an increase in drug effect
- Also, body fat increases creating a larger volume of distribution for lipophilic drugs (very little significance clinically)
Drug Metabolism

- Some enzymes of the hepatic Cytochrome p-450 are induced, this causes a higher rate of metabolism
- Some extra-hepatic enzymes, such as cholinesterase, have diminished activity during pregnancy
Drug Elimination

- Renal blood flow is increased by 50-60% during pregnancy
- GFR rises by approx. 50% leading to enhanced elimination of drugs
How Drugs Affect the Fetus?

1. Drugs can act directly on the fetus causing damage or abnormal development—Birth defects—Death
2. They can alter the function of the placenta
3. Can cause the muscles of the uterus to contract forcefully.
What about our breastfeeding pts?
What about our breastfeeding pts?

- Nearly all drugs transfer into breast milk to some extent
- The infant is considered an “innocent bystander”
- Majority of drugs cross from maternal plasma into breast milk
- Most medications found in very small amounts in breast milk
- Risk of adverse effects in nursing infants is negligible for most drugs
General Considerations (Fultz, 1999)

1. Use drug therapy when necessary
2. Avoid drugs with active metabolites (meperidine)
3. Schedule doses immediately after nursing or prior to infant`s longest sleep period
4. Monitor infant`s drug plasma levels when using more toxic drugs, when there is a concern about infant`s dose or evidence of side effects.
Which drugs can I prescribe to my pregnant Pts?
To determine the risks associated with the use of drugs in pregnancy, the United States Food and Drug Administration (FDA) classified prescription drugs based on fetal injury risk.
# FDA Classification System

<table>
<thead>
<tr>
<th>FDA Category*</th>
<th>Pregnancy Category Definition</th>
</tr>
</thead>
</table>
| A             | Controlled studies showed no risk to humans  
                Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities |
| B             | No evidence of risk in humans  
                Animal studies have revealed no evidence of harm to the fetus. However, there are no adequate and well-controlled studies in pregnant women  
                or  
                Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus |
| C             | Risks cannot be ruled out in humans  
                Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women  
                or  
                No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women |
| D             | Clear evidence of risk in humans  
                Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus.  
                However, the benefits of therapy may outweigh the potential risk |
| X             | Drugs contraindicated in human pregnancy  
                Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant |
FDA Classification System

A: No risk to the fetus
B: No risk to the fetus But there are no adequate and well-controlled studies in pregnant women
C: Adverse effect on the fetus on animals, but there are no adequate and well-controlled studies in humans. Consider Potential benefits v. potential risks
D: Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. Consider Potential benefits v. potential risks
X: Studies in humans or animals have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the agent in pregnant women clearly outweigh the potential benefits.
Specific drug groups

1. LA
2. Analgesics
3. Anti-infectives
4. Sedatives
Local Anaesthetics
Considered safe during pregnancy
Considered safe during breastfeeding
LA are not teratogenic (may administer with the usual dose)
Lidocaine, prilocaine and etidocaine--- FDA ranking B
What about Epi?
Epinephrine

- Potential to compromise uterine blood flow
  - Studies have failed to demonstrate adverse fetal effects
  - Low doses used in dentistry
  - Avoid intravascular injections

- Careful Aspiration
- Slow injections
- When concern: 1:200,000 epi
Acetaminophen

- Analgesic of choice
- Most frequently used
- No teratogenesis
- FDA ranking---B
- Can be used for our breastfeeding pts
**NSAIDs**

The use of NSAIDs is less favourable

NSAIDs reduce the synthesis of PG and therefore may cause an increase in bleeding

Some data demonstrate that Aspirin may cause oral clefts and other defects
Use of NSAIDs in pregnancy increases risk of miscarriage (BMJ 2001:322:266-270)
ASA has been associated with bleeding complications in the newborn
DO NOT use the third trimester

WHY?
Increase bleeding
Prolonged labour
Premature closure of ductus arteriosus
ASA is given a FDA category C (for first and second trimesters)

FDA Category D in the third trimester

Alternative Analgesics should be used

THM: Avoid using it if by all possible
What about our lactating Pt?

- Aspirin may increase bleeding by interfering with the infant`s platelet function
- Avoid if by all possible
- Other NSAIDs?
- Avoid, if need, please Rx short-acting NSAIDs e.g. Ibuprofen
NARCOTICS

Codeine

Unlikely to pose substantial teratogenic risk but data insufficient to state no risk
Association between 1st trimester use and congenital anomalies in case control studies
Chronic use may result in fetal dependence and premature delivery
Codeine has FDA Category C
May be used in 2nd and 3rd trimester (DO NOT use in 1st trimester)
If used, low doses and short duration
Oxycodone (Percocet, Percodan), hydromorphone and meperidine (Demerol) have not been associated with congenital defects

All have FDA Category B

May be used

As with Codeine, Low therapeutic doses and short duration
• What about our lactating Pt?
• Codeine- ??? can be used (may cause drowsiness, especially in neonates)
• Meperidine- try to avoid as it is found in high concentration in breast milk
• Morphine- can be used

General
• Eliminate the source of pain, if at all possible.

For Acetaminophen:
• Acetaminophen is the analgesic of choice in the otherwise healthy pregnant patient.
• Use a dose of 500 – 1,000 mg every 4 hours to a maximum of 4 grams per day.

For NSAIDs:
• NSAIDs can be used cautiously in first and second trimesters.
• NSAIDs should be avoided during the third trimester.
• If NSAIDs are used in the pregnant patient, it is recommended to use the lowest effective dose for as short a period of time as possible.

For Opioids:
• Opioid analgesics can be cautiously prescribed to the pregnant dental patient.
• If opioid analgesics are prescribed, low dose and short duration are recommended.
Anti Infectives
General Guidelines

- Generally safe
- Antibiotics are not a substitute to I & D
- Normally, if I & D are not satisfactory (fever and/or extensive swelling)
Penicillin

- FDA--- B
- Safe in all trimesters
- No teratogenic

- Amoxicillin and cephalosporins also considered safe to use during pregnancy
- Amoxicillin and cephalosporins also considered safe to use during breastfeeding
- No increase risk of malformations with amoxicillin-clavulanic acid (Clavulin) in several studies (Br J Clin Pharmacol 2004 and Eur J Obstet Gynecol Reprod Biol 2001)
Erythromycin

- FDA Category B
- Do not use the estolate form because it may cause cholestatic hepatitis
Tetracycline

- Usually not the drug of choice for oro-facial infections
- May be used for periodontal infections
- FDA Category D
  - Tetracycline or doxycycline whether administered systemically or subgingivally are CONTRAINDICATION DURING PREGNANCY
Metronidazole

- Used for periodontal conditions
- FDA category B
- Small number of reports raised suspicion of teratogenic effect
- USE CAUTIOUSLY
Metronidazole and the Lactating mother

- The use of metronidazole during lactation is controversial.
- Excreted into breast milk in relatively high amounts.
- Concern expressed of adverse effects in nursing infants.
- THM: USE CAUTIOUSLY.
Other Antibiotics which we may use

- Clindamycin (FDA category B)
- Azithromycin (FDA category B)
What about Chlorhexidine rinse?

- FDA Category B
- SAFE TO USE FOR PREGNANT WOMEN
- SAFE TO USE FOR Lactating mother
Antifungals

Nystatin- FDA Category B

Ketoconazole- FDA Category C (use cautiously)

Fluconazole- FDA Category C (use cautiously)
SEDATIVES
Nitrous Oxide
The use of Nitrous oxide during pregnancy is controversial.

In animal studies, nitrous oxide has been shown to inhibit methionine synthase, which can affect DNA synthesis.

The anomalies associated with nitrous oxide were previously thought to occur from inhibition of methionine synthase.
Evidence demonstrated that this may not be true in humans (Garrison et al., 1989)

Because short-term therapeutic exposure to nitrous oxide has not been proven to cause any adverse effects, it may be used in pregnant pts (Garrison et al., 1989; Crawford and Lewis, 1986)

We have another issue: Chronic exposure to nitrous oxide by pregnant dental personnel
The situation has been linked to infertility, congenital malformations and spontaneous abortions (Rowland et al., 1992; Meshkin, 1993; Rowland et al., 1995)

To prevent chronic exposure in the dental office, it is important to monitor the nitrous oxide levels (proper scavenging equipment, checking regularly for leaks, appropriate operatory ventilation etc...
So what do we do?

1. Do not administer nitrous oxide unless it is absolutely necessary
2. DO NOT USE in the 1\textsuperscript{st} trimester
3. If given (in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters), it should be administer for less than 30 mins
4. Use at least 50 % Oxygen
5. No concern during breastfeeding
Benzodiazepines
• Use of Benzodiazepines during pregnancy is controversial
• Previous studies have linked the use of BZDs to major malformations such as craniofacial defects (e.g. oral clefts)
• BZDs have also been linked to causing fetal CNS depression
• Diazepam, lorazepam and midazolam have FDA category D
• Avoid Rx BZDs
What about the breastfeeding mother?

- BZDs should be avoided during breast-feeding as significant sedation may result
- DO NOT use diazepam
- If need, short half-life such as clonazepam and midazolam are preferred (Short term only)
Geriatric Pharmacology
Pharmacotherapy for the Elderly Dental Patient

Aviv Ouanoounou, MSc, DDS, FICO; Daniel A. Haas, DDS, PhD, FRCD(C)

Posted on September 25, 2015

Tags: anesthesia, pain, pharmacology, seniors

Cite this as: J Can Dent Assoc 2015;80:f18

ABSTRACT

Current demographic data clearly show that the North American population is aging, and projections suggest that the proportion of older people will increase. The elderly often suffer from multiple chronic conditions that affect their general health and quality of life. In those of advanced age, the pharmacokinetics and pharmacodynamics of drugs can differ from those of younger patients. This may lead to changes in their response to medications. Therefore, it is important to consider the patient's age, comorbidities, and medications when selecting and administering drugs to elderly dental patients. The use of non-pharmacological interventions, such as local anesthetics and analgesics, can be effective in managing pain and discomfort during dental procedures. Additionally, the use of appropriate dosing and monitoring of elderly patients can minimize the risk of adverse drug reactions.
Number of people aged 60 and over

Source: UN, 2002
• This population accounts for over 35% of Rx
• 2-6 prescribed medications and 1-3 non prescribed
• 20% of geriatric hospitalizations are due to medications problems
ADVERSE DRUG REACTIONS

DRUG-DRUG INTERACTIONS
WHY in the Elderly?

- Complex drug therapies
- PK changes
- PD changes
- Non-adherence
- Cognitive problems
- Co-morbidity
POLY-PHARMACY
Affects about 1 in 3 people over the age of 65

Significant cause of death in the elderly

May be the 3rd or 4th leading cause of death in North American elderly

Causes...
Physiological changes associated with aging affects PK and PD
PHARMACOKINETICS
ABSORPTION

- Decreased Gastric acid secretion
- Decreased Gastric emptying
- Slower GI motility
Geriatric pts may be prone to other factors that alter drug absorption

1. Swallowing difficulties
2. Poor nutritional status
3. Erratic meal patterns
4. GI conditions
OVERALL:

Absorption is not a significant factor
DISTRIBUTION

- Decrease in total body water
- Decrease lean body mass (decrease the volume of the drugs that bind to muscle)
- Increase in Fat stores
- Decrease in plasma Albumin
- Increase in alpha1-acid glycoprotein
● This will result in increase concentrations of drugs that are water soluble

● Drugs that are highly protein bound will have a higher free drug level where albumin levels have decreased
Aging Effects on Hepatic Metabolism

Metabolic clearance of drugs by the liver may be reduced due to:
1. Decreased hepatic blood flow (delay metabolism and increase toxicity)
2. Decreased liver size and mass
ELIMINATION

- Decreased kidney size
- Decreased numbers of functional nephrons
- Renal function decreases with age (10% every year beginning in the forth decade)
- GFR (glomerular filtration rate) decreases with age
- Renal plasma flow decreases with age
How these factors affect my decisions when administering and prescribing drugs
As Dentists:

- LA
- Analgesics (Acetaminophen, NSAIDs, Opioids)
- Anti- infectives
Local Anaesthetics

- No significant differences
- Aging is accompanied by increased liver and kidney disease and thus it is recommended to stay well below the maximum doses.
- Vasoconstrictors (CVS)
- It is recommended to limit the doses of epinephrine, such as to a maximum of 0.04 mg.

OPIOID ANALGESICS

- Increase depth
- Increase duration
- Concurrent CNS drugs

Increase in the susceptibility to side effects e.g. constipation, dizziness, agitation, urinary retention and respiratory depression
Meperidine

- Analgesic of choice for acute and severe post-op pain
- PK and PD changes associated with aging result in substantial risks when the drug is used in elderly pts
- It has been associated with anxiety, tremors and seizures
- THM: AVOID Rx this Drug
Whenever possible:

- Opioid analgesics should not be used in our elderly pts
- If it is needed, reduce the dose by half and monitor the pt.
NSAIDs

[Image of aspirin and ibuprofen bottles]
NSAIDs

- The high frequency of NSAIDs use in the elderly population is due to the high prevalence of chronically painful conditions such as osteoarthritis.
- An estimated 15% of individuals older than 65 have a current or recent Rx for a NSAID (Griffin et al., 1991)
**NSAIDs**

- Highly lipid-soluble drugs with extensive protein binding
- This may result in widespread distribution in elderly persons due to increase adipose tissue stores
- Elderly person also have an increased concentration of unbound drug due to reductions in plasma protein found in many older persons
- Also, many elderly persons have reduced renal function, NSAIDs have decreased renal clearance in older pts, potentially resulting in excessive drug levels and toxicity
NSAIDs can affect GI, renal, CV, CNS and hematologic systems.

- Adverse effects are more common:
  Increased bleeding, Dyspepsia, Gastric mucosal damage, Renal impairment
Avoid the use of NSAIDs if Hx of gastric bleeding or ulcer
Avoid if Pt is taking multiple NSAIDs
If Rx, reduce the dose and avoid the use of 2 or more NSAIDs.
If a NSAIDs is needed, Ibuprofen is a good first choice. Add the anti-ulcer drug misoprostol (Cytotec) if prescribed for more than 4 days or immediately if the pt has an ulcer history.
Alternatives to NSAIDs should be tried before giving the elderly pts long term NSAIDs therapy

Acetaminophen
- Absorbed rapidly
- No gastric mucosa effects
- No effect on platelets aggregation
- Metabolized in the liver
- Excretions urine (metabolites can accumulate with renal impairment)
- Hepatotoxic
In healthy Elderly pts doses do not have to be altered

If Alcoholism, therapeutic doses can cause hepatotoxicity
Acetaminophen in the elderly has proven to have broad tolerability, reasonable efficacy and a low side effect profile.

- Very little drug interactions (very important in this population)
- The analgesic of choice
Anti-infectives
There are no specific changes in the therapeutic use and dose of anti-infectives in our elderly healthy pts. However, doses may need to be reduced because of decreased lean body mass, especially older women. Also, there are number of potential drug interactions that may lead to modification of the anti-infective that we select.
Examples

- Cephalothin can cause nephrotoxicity at high doses
- Erythromycin can cause ototoxicity if impaired renal function is present.
- Clindamycin can increase the incidence of GI problems such as diarrhea and colitis.
- Clarithromycin (and Clindamycin) may interact with digoxin (this Anti-infective may decreases the clearance of digoxin from the body)
- Metronidazole and Ciprofloxacin will increase the anticoagulant effect of Warfarin by decreasing its hepatic metabolism.
Table 3: General recommendations for the use of analgesics in elderly patients.

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate the source of pain, if at all possible.</td>
</tr>
<tr>
<td>• Prescribed doses should be based on pain severity and medical history.</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>• Acetaminophen is the analgesic of choice in the otherwise healthy elderly patient.</td>
</tr>
<tr>
<td>• Use a dose of 500–1000 mg every 4 h to a maximum of 4 g/day.</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
</tr>
<tr>
<td>• NSAIDs are best avoided by elderly patients because of associated increased gastrointestinal problems.</td>
</tr>
<tr>
<td>• If NSAIDs are prescribed, use the lowest effective dose for the shortest possible time.</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>• Opioid analgesics are best avoided by elderly patients because they are associated with increased and more profound adverse drug reactions as well as prolonged durations of action.</td>
</tr>
<tr>
<td>• If opioid analgesics are prescribed, the dose should be lower than that for younger adults.</td>
</tr>
</tbody>
</table>

“Pharmacotherapy for the Elderly Dental Patient”
Ouanounou, A and Haas, D.  JCD A. 2015
How to avoid ADRs in our elderly pts?

1. Medical Hx
2. Accurate Dx
3. Critical assessment of the need of pharmacotherapy
4. Understand which specific drugs have the greatest probability of causing ADRs (e.g. anticoagulants, anticonvulsants, Cardiac meds)
5. Understand the drugs used commonly in dentistry, their metabolism, effects, side effects and toxicities.
Summary:

1. Never administer or prescribe a drug without an indication (does the pt needs the drug?) (e.g. antibiotics for the prevention of infective endocarditis).
2. Balance the risks and benefits of administering or prescribing any drug
3. Proceed only if the balance is favorable
4. Drugs not a magic bullet, they are always associated with ADRs and DIs
THANK YOU