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ANALGESICS

NON-OPIOID ANALGESICS
COX-1 AND COX 2

- COX-1 CONSTITUTIVELY EXPRESSED
  - GOOD THINGS – KIDNEY PERFUSION, ANTI-COAGULATION, VASODILATION, GI PROTECTION

- COX-2 INDUCED BY:
  - CYTOKINES, GROWTH FACTORS, ENDOTOXIN
  - LEADS TO INFLAMMATION CASCADE
NSAIDs

- ANALGESIC
- ANTI-INFLAMMATORY
- ANTIPYRETIC
- INHIBIT CYCLOOXYGENASES
  - Prostaglandins
  - Thromboxanes
WHY NSAIDS?

• LACK UNWANTED SIDE EFFECTS OF THE OPIOIDS ON THE CNS

  • RESP. ↓ & PHYSICAL DEPENDENCE

• DO NOT CHANGE THE PERCEPTION OF SENSORY MODALITIES OTHER THAN PAIN

• CHRONIC POST-OP PAIN OR PAIN FROM INFLAMMATION IS WELL CONTROLLED BY NSAIDS
NSAIDs

- PIROXICAM (FELDENE)
- SULINDAC (CLINORIL)
- KETOROLAC (TORADOL)
- FLURBIPROFEN (ANSAID)
- DICLOFENAC (CATAFLAM)
- IBUPROFEN (MOTRIN)
NSAIDS (COX-2)

- NABUMETONE (RELAFEN)

- CELECOXIB (CELEBREX)

- MELOXICAM (MOBIC)

- GONE
  - ROFECOXIB (VIOXX)
  - VALDECOXIB (BEXTRA)

- COMING SOON
  - LUMIRACOXIB (PREXIGE)
  - ETORICOXIB (ARCOXIA)
NSAID INTOLERANCE

● CROSS HYPERSENSITIVITY
  • USUALLY NOT IgE MECHANISM

● SHUNTING TOWARDS LEUKOTRIENE SYNTHESIS
  • BRONCHOSPASM & ANAPHYLAXIS

● DO NOT USE ANOTHER NSAID
  • USE ACETAMINOPHEN
ASPIRIN VS CODEINE

- ASPIRIN 650 mg. MORE EFFECTIVE THEN CODEINE 30mg.
  - Clinical Pharmacology Therapy 1976
  - MORE ANALGESIC EFFICACY
  - LESS SIDE EFFECTS
IBUPROFEN 400 mg.

- SUPERIOR TO:
  - ASPIRIN 650 MG
  - ACETAMINOPHEN 1000MG.
  - COMBINATIONS OF ASA/ACETAMINOPHEN AND CODEINE 60 MG.
IBUPROFEN 400 mg.

- SUPERIOR TO 30 MG. DIHYDROCODEINE
- COMPARABLE TO ALL OTHER NSAIDS
- FEWER SIDE EFFECTS
NSAIDs

- PRE-EMPTIVE ANALGESIA

- INHIBITS THE “FORMATION” OF PROSTAGLANDINS

- HAVE ON BOARD BEFORE START
  - Jackson, Moore, JADA 1989
**NSAID CONTRAINDICATIONS**

- **CURRENT HX**
  - NEPHROPATHY
  - EROSIIVE ULCERATION OF GI
  - ANTICOAGULANT TX
  - HEMORRHAGIC DISORDER

- **PRIOR HX OF NSAID/ASA ALLERGY OR INTOLERANCE**

- **CONCURRENT ANTIHYPERTENSIVE THERAPY (RELATIVE)**
NSAIDS AND KIDNEY

- LITTLE EFFECT ON RENAL FUNCTION IN NORMAL PATIENT – FOR SHORT TERM USE

- ↓ RENAL FLOW IN:
  - CHF, CIRRHOSIS, CHRONIC RENAL DISEASE, HYPOVOLEMIA

- PROMOTES SALT AND H2O RETENTION

- REDUCES PGE2 -INDUCED INHIBITION OF BOTH THE REABSORPTION OF CHLORIDE AND ACTION OF ADH

  - CAUSES EDEMA

  - REDUCES EFFECTIVENESS OF ANTI-HYPERTENSIVES AGENTS
NSAIDS AND KIDNEY

- BINDING OF PGI2, PGE1, AND PGD2 TO PLATELET RECEPTORS ACTIVATES GS (↑cAMP – ACTIVATES KINASES – THE KINASES PHOSPHORYLATE INTERNAL CALCIUM PUMP PROTEINS - ↓FREE INTRACELLULAR CA2+ CONCENTRATION = VASODILATION

- BINDING OF TXA2 TO ITS RECEPTORS (GQ) ACTIVATES PHOSPHATIDYLINOSITOL METABOLISM – LEADING TO FORMATION OF IP3, - IP3 BINDS TO CALMODULIN AND ↑INTRACELLULAR Ca2+ = VASOCONSTRICTION
PLATELETS AND BLOOD CELLS

- PGE$_1$ & ESPECIALLY PGI$_2$ – INHIBIT PLATELET AGGREGATION

- TXA$_2$ IS A POTENT PLATELET AGGREGATOR

- PLATELETS RELEASE TXA$_2$ DURING ACTIVATION AND AGGREGATION
RENAL MEDULLA (1°) AND CORTEX SYNTHESIZE PROSTAGLANDINS

PROSTAGLANDINS = REGULATION

RENAL CORTEX – PGE₂ AND PGI₂ - ↑ RENIN RELEASE

PGE₁, PGE₂, & PGI₂ ↑ GLOMERULAR FILTRATION VIA VASODILATING EFFECTS
NSAID SIDE EFFECTS

• ↑ BP (FLUID RETENTION)

• DIZZINESS

• RASH

• GI IRRITATION (ULCER)

• RENAL PAPILLARY NECROSIS + OTHER RENAL MEDULLARY CHANGES

• LICHEN PLANUS
IBUPROFEN TOXICITY

- $T_{1/2}$ 2 HR.
- 400 mg. PEAK PLASMA LEVEL 29 ug/ml IN 90 MIN.
  - 3ug/ml IN 8 HR.
  - NON DETECTED IN 12 HR.
- 17 CHILDREN 2.4 g. ASYMPTOMATIC
- 13 ADULTS UP TO 24 g. NO ILL AFFECTS
NSAIDs and Bone

Aspirin: irreversible inhibition of COX-1 and COX-2

Non-specific NSAIDs: reversible inhibition of COX-1 and COX-2
(indomethacin, ibuprofen, diclofenac, naproxen, nambutone)

COX-2 specific inhibitors: reversible inhibition of COX-2
(celecoxib, rofecoxib, valdecoxib)
In a retrospective study of 83 patients undergoing spinal fusion, those patients who postoperatively used NSAIDs for longer than 3 months showed only 37% fusion rate compared to a 93% fusion rate in patients not taking NSAIDs.

COX-2 Effects on Fracture Healing

- The healing of stabilized tibia fractures was delayed in COX-2 knockouts compared to wild-type animals and to COX-1 knockouts.

- In radiographic analysis at 21 days post-fracture normal healing found in:
  - 8 out of 10 wild-type mice
  - five out of six COX-1 knockouts
  - three out of eight COX-2 knockouts

Indomethacin vs. Coxibs on fracture healing

- Celecoxib or Rofecoxib evaluated in femur fracture in rats
- All three drugs inhibited fracture healing
- 8 week results healed:
  - Control 7/7
  - Indomethacin 6/8
  - Celecoxib 0/6
  - Rofecoxib 0/5
Acetaminophen vs. Celecoxib
Femur fracture repair in rats

• Acetaminophen - no delayed healing

• Celecoxib - impaired healing when observed at 8 weeks

Bone formation process

- Ostoclasts ➔ resorption ➔ free up BMPs
- BMPs ➔ osteoblasts ➔ bone formation
Prostaglandins & bone formation

• PGs ↑ # and activity of osteoclasts = bone resorption

• PGs ↑ replication and differentiation of osteoblasts = bone formation

• PGs ↑ blood supply through vasodilation & ↑ angiogenesis

  • Raisz LG. Prostaglandins and bone: physiology and pathophysiology. Osteoarthritis Cartilage 1999;7:419-21

Cylooxygenases

- COX-1: expressed in normal bone and at bone fracture sites
- COX-2: up-regulated during initial stages of bone repair
- Osteoclasts and osteoblasts produce PGs (PGE$_2$)
Pharmacology Principles

- Dose
- Route of administration
- Duration
Glucocorticosteroids

• Long-term chronic use ↓ COX-2 expression and therefore PG production

• Result: Bone loss
NSAIDs

- Therapeutic effect achieved by inhibition of COX-2
- Selective COX-2 inhibitors reduce risk of GI adverse events
- ? - Will these drugs impact bone healing
Effects of prostaglandins on the bone fracture healing process
- prostaglandins contribute to the early inflammatory response to trauma as proinflammatory and hyperalgesia-inducing mediators
- prostaglandins support blood supply to the fracture site by enhancing blood flow and by promoting angiogenesis
- prostaglandins (especially PGE₂) increase the number and activity of osteoclasts and subsequent bone resorption
- prostaglandins (especially PGE₂) stimulate bone formation by increasing replication and differentiation of osteoblasts
Abundant experimental data suggest that non-selective NSAIDs delay fracture healing. (Vuolteenaho K, et al. Non-steroidal Anti-Inflammatory Drugs, Cycloxygenase-2 and the Bone Healing Process)
A-HA study

- Non-selective naproxen and Cox-2 selective rofecoxib - harvest chamber implanted in rat tibia
- ↓ bone formation observed at 4 weeks
- Effect was dependent upon duration of treatment
  - 2 week course at the beginning or at the end of a 6 week harvest period did not inhibit bone ingrowth to the same degree as did continuous treatment (Pharmacology principle)

Semi-selective COX-2

- Etodolac at 3 time frames
  - Group 1: treatment for the entire 3-week duration
  - Group 2: treatment for the first week
  - Group 3: treatment for the final third week
- Results: Impaired healing for groups 1 and 2 only

Celecoxib - Treatment time

• Impaired femoral fracture healing in rats when administered during the first 2 weeks after fracture

• No significant effect when administered starting 14 days later

Selective and nonselective cyclooxygenase-2 inhibitors and experimental fracture-healing. Reversibility of effects after short-term treatment

- ED50 doses used of ketorolac (non-selective) and valdecoxib (COX-2 selective) for either 7 or 21 days after fracture in rats

- 7-day treatment produced a trend for nonunion fracture healing for both ketorolac and valdecoxib

- 21-day treatment produced significantly more non unions in the valdecoxib group vs ketorolac or controls

- PGE2 levels decreased but if drugs d/c after 6 days the levels of PGE2 rebounded 2-fold by day 14

Flurbiprofen - a friend

• The Effect of Systemic Flurbiprofen on Bone Supporting Dental Implants. Jeffcoat MK et al. JADA Vol 126 March 1995: 305-11

• Observed alveolar bone changes surrounding mandibular dental implants in 29 patients at 6, 9, and 12 months after implant placement to determine the effect of the flurbiprofen treatment on the implant's success or failure

• Digital subtraction radiography as measurement tool

• Group 1: placebo BID

• Group 2: 50 mg flurbiprofen BID

• Group 3: 100 mg flurbiprofen BID

• Dosing began on day of implant surgical placement
Results

- Significant changes in bone height occurred following exposure and loading of the implant, between the 3rd and 6th months of the study.
Results

Figure 2. Cumulative bone loss on the mesial surface of the implants. Bone loss is measured as the change in bone height in millimeters.
Results

Figure 3. Cumulative bone loss on the distal surface of the implants. Bone loss is measured as the change in bone height in millimeters.
Results

Figure 4. Cumulative change in bone mass expressed as the change in bone mass in milligrams.
Conclusion

- The basic pathophysiology and pharmacokinetics underlying the effect(s) of NSAIDs on bone could be used to support either positive or negative effects on bone.

THINK ABOUT THIS:

- Excessive PGE2 formation can result in bone loss
- Controlling PGE2 formation may be good
- However, PGE2 in the right concentration promotes bone formation
- What should we do?
Conclusion

- This study provides preliminary data that suggest that systemic administration of flurbiprofen may reduce bone loss around dental implants in the first year of service.
Although animal studies raise theoretical concerns, no conclusive evidence supports denying patients the analgesic benefits of NSAIDs for managing fractures.

## Table

<table>
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<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Randomized controlled trial*</td>
<td>Postmenopausal women with Colles’ fractures (N=42)</td>
<td>Piroxicam</td>
<td>No delay in fracture healing</td>
</tr>
<tr>
<td>Retrospective*</td>
<td>Patients with long-bone fractures (N=112)</td>
<td>Indomethacin</td>
<td>Rate of nonunion 29% vs 7% (P=0.004)</td>
</tr>
<tr>
<td>Retrospective*</td>
<td>Patients with femoral shaft fractures (N=99)</td>
<td>Diclofenac or ibuprofen</td>
<td>OR for nonunion=10.7 (95% CI, 3.5-33.2)</td>
</tr>
<tr>
<td>Retrospective*</td>
<td>Postoperative spinal fusion patients (N=288)</td>
<td>Ketorolac</td>
<td>OR for nonunion=4.9 (95% CI, 1.8-16.6)</td>
</tr>
<tr>
<td>Retrospective*</td>
<td>Patients with tibial fractures (N=94)</td>
<td>Multiple NSAIDs</td>
<td>Increased mean time to union of 7.6 wk (P=0.003)</td>
</tr>
<tr>
<td>Retrospective*</td>
<td>Patients with humeral shaft fractures (N=9995)</td>
<td>Multiple NSAIDs</td>
<td>Increased risk of nonunion with exposure to NSAIDs 60-90 days postfracture (RR=3.9, 95% CI, 2.0-6.2)</td>
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</table>

CI, confidence interval; OR, odds ratio; RR, relative risk.

Although animal studies raise theoretical concerns, no conclusive evidence supports denying patients the analgesic benefits of NSAIDs for managing fractures.


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**References**


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Visit us online at [jfponline.com](http://jfponline.com)
Case: 62 yr. Old Caucasian Osteoarthritis

- Meloxicam (Mobic™) 15 mg/day for past 3 years

- Mechanism of Action: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; 10:1 preference for COX-2 over COX-1
Agents with Periodontal Regenerative Potential Regulate Cell-mediated Collagen Lattice Contraction in vitro


• In vitro study that examined effects of TGF-β1, PDGF, and IGF-1; indomethacin ibuprofen, naproxen, and flurbiprofen; and alcohol on cell-mediated gel contraction

• Represents in vivo wound contraction and remodeling

• Results:
  • TGF-β1, PDGF, and IGF-1 promoted cell-gel contraction - similar to wound healing
  • NSAIDs inhibited cell-gel contraction
  • Alcohol inhibited cell-gel contraction
NSAIDs and Bone

NSAIDs

Arachidonic Acid

PRP
IL-1α

TGF-β1
PDGF-BB
VEGF
OPG

PGE₂

Bone Formation

Chronic

X
X
X
X

James L. Rutkowski, D.M.D., Ph.D.
Clinical Suggestions

• Limit routine NSAID use to 5 days thereafter PRN and/or switch to Acetaminophen with/without narcotic

• Use a non-specific COX inhibitor

• Use PRP
Chronic NSAID Use

• Use Flurbiprofen 50 – 100 mg twice a day
  • Bone. 1989;10(1):35-44
  • J Oral Implantol. 1990;16(4):272-6

• Monitor patients blood pressure

• Take “Drug-Free” holidays
• MOST DENTAL PAIN IS DUE TO INFLAMMATION

• NSAIDS HELP PREVENT THIS CASCADE

• 1ST LINE OF ANALGESIA

• OFTEN SUPERIOR TO OPIOIDS

• IF CONTRA. THEN ACETAMINOPHEN
ASA DOSE FOR MI/STROKE PREVENTION

• 81 MG. INHIBITS THROMBOXANES, BUT NOT PROSTACYCLIN (PGI₂)

• SO PREVENTS CLOTTING AND STILL ALLOWS VASODILATION AND PREVENTION OF PLATELET CLUMPING
ASA DOSE DURING MI

- 325 MG. PREVENTS CLOTTING BY THROMBOXANES

- BUT THERE IS MUCH MORE TBX$_2$ DUE TO RELEASE FROM MONCYTES AND EOSINOPHIFS
ACETAMINOPHEN

- PROSTAGLANDIN PATHWAYS IN CNS - COX-3 INHIBITOR

- LITTLE PERIPHERAL INFLUENCE

- LITTLE ANTI-INFLAMMATORY

- NONE OF NSAID PERIPHERAL SIDE EFFECTS
ACETAMINOPHEN

• ONLY INHIBITS CYLCOOXYGENASE IN AREAS OF LOW PEROXIDE FORMATION

• HYPOTHALAMUS

• SITES OF INFLAMMATION USUALLY HAVE HIGH PEROXIDES GENERATED BY LEUKOCYTES

• REF. MARSHALL 1987
ACETAMINOPHEN

• EQUAL IN POTENCY AND EFFICACY TO ASPIRIN

• ∴ INFERIOR TO IBUPROFEN AND OTHER NSAIDs
ACETAMINOPHEN

• HEPATOTOXICITY

• TOXIC DOSE 10-15 Grams

• LOWER TOXICITY IF:
  • DEPLETED GLYCOGEN
    • CHRONIC ALCOHOLISM MAX. DAILY DOSE IS 2 Grams VS NORMAL 4 Grams
The enzyme that metabolizes acetaminophen to its toxic metabolite is CYP2E1. This same enzyme metabolizes ethanol. Ethanol can increase CYP2E1 and decrease Glutathione concentrations, potentially leading to more NAPQI formed.

Hass D. Adverse Drug Interactions in Dental Practice. JADA 1999;130:397-407

NAPQI=Toxic!
NAPQI + Glutathione = Non-toxic

Chronic alcohol consumption = ↑ CYP2E1, ↓ Glutathione

Alcohol + Acetaminophen = NAPQI

↑↑ NAPQI Hepatotoxicity
1. Which Cyclooxygenase enzymes provide prostoglandens that result in good things when they land on their receptors?

A. Cox-1
B. Cox-2
C. Cox-3
D. Cox-4
You are planning to do an all-on-4 procedure for a 72 year old female patient who takes Celebrex BID. How should this drug be managed during the surgical phase?

A. Discontinue the Celebrex one week prior to the surgery and for at least 2 weeks post-operatively

B. Discontinue the Celebrex on the day of surgery, but restart after 3 days.

C. Make no changes in the patients Celebrex use

D. D/C the Celebrex and put the patient on oxycodone for the arthritic pain and Colace for the constipation
3. Your 58-yo patient presents with an abscessed mandibular left 1st molar and he rates the pain as a 10 on the scale of 1-10. He has a history of drinking 4 to 6 Bud Lights each evening. He also takes Paxil (SSRI) and Tagamet. The best pain medication for this patient is:

A. An NSAID plus acetaminophen 1 gram every 6 hours and have him stop drinking the alcohol

B. Oxycodone with acetaminophen and have him stop drinking the alcohol

C. Hydrocodone with acetaminophen 1 gram every 6 hours and have him continue drinking the alcohol

D. An NSAID plus acetaminophen 500 mg every 6 hours and have him continue drinking the Bud Light
ANALGESIC PROTOCOL

- NON-OPIOIDS AND OPIOIDS
ANALGESIC REGIMENS

- **STEP 1**
  - START WITH IBUPROFEN 600 MG. ONE HOUR PRE-OP

- **STEP 2**
  - CONTINUE IBUPROFEN 600 MG. Q 6 HRS FOR 3-5 DAYS OR FLURBIPROFEN 100 MG BID FOR 3 TO 5 DAYS

- **STEP 3**
  - IF IBUPROFEN IS NOT CONTROLLING PAIN THEN ADD ACETAMINOPHEN 500-1000 MG. Q 6 HRS.
ANALGESIC REGIMENS

- **STEP 4**
  
  - ADD A NARCOTIC + ACETAMINOPHEN COMBINATION DRUG (i.e. Lortab 10/500) one or two tablets q 4 to 6 hrs as needed.
  
  - Discontinue the previously prescribed individual acetaminophen
ANALGESIC ADJUVANTS

- TRI-CYLIC AND ATYPICAL ANTIDEPRESSANTS HAVE BENEFIT
- TRAMADOL (ULTRAM)
  - OPIOID AND ANTIDEPRESSANT
  - PARENT DRUG LIKE TRI-CYLIC ANTIDEPRESSANT
  - METABOLITE –m1- WEAK AGONIST ON MU RECEPOTRS
  - GOOD FOR CHRONIC PAIN
ANALGESIC ADJUVANTS

- CAFFEINE

- INCREASES POTENCY OF ASA & TYLENOL, BUT NOT THE EFFICACY
ANALGESIC ADJUVANTS

• SEDATIVE/ANXIOLYTICS
  • NO BENEFIT TO ANALGESIC EFFICACY

• ANTIEMETICS
  • USE TO TX N & V OF OPIOIDS
  • CANNOT PREVENT N & V OF OPIOIDS
ANTIBIOTICS

- MANAGE ORO-FACIAL INFECTIONS
- PROPHYLAXIS
Antibiotic Usage
Reference: Pharmacology and Therapeutics for Dentistry

• Most widely abused prescribed drugs on the basis of
  • Inappropriate indications
  • Inappropriate dosages
  • Duration of use
Questions - we need answers

1. What are the empiric antibiotics of choice
   1.1. contemporary double blinded trial comparing all of the relevant antibiotics in a large, multicenter, North American population of patients with well-defined OI, combined with appropriate surgical treatments, would be ideal

2. How long should the treatment choice last?
   2.1. study of the duration of the antibiotic treatment course, with its long-term effects on selection for antibiotic-resistant bacteria, would provide the answer

Antibiotic Usage

- 1/2 all antibiotics given in hospitals are to patients without signs of infection
- Mainly to prevent infections
- To cover errors of omission or commission
- Prevent a claim of negligence

- Reference: Pharmacology and Therapeutics for Dentistry
Antibiotic Usage

- “80:80” rule: 80% of the antibiotics are used in the community and of that 80% are used for respiratory infections.

- Of the 50% of the patients with acute respiratory illness - 80% receive an antibiotic - however, pneumonia is the only respiratory disorder that requires and antibiotic accounts for only 2% of the cases.
Antibiotic Usage - Dentistry

• Dentists prescribe 7 to 11% of all common antibiotics: β-lactams, macrolides, tetracycline, metronidazole, clindamycin

• England: 33 to 87% antibiotic usage by Dentists deemed unnecessary
Inappropriate Antibiotic use in Dentistry

1. Initiated after surgery to prevent an infection unlikely to occur

2. Failure use antibiotics according to the principles established

3. Used as analgesics in endodontics
Inappropriate Antibiotic use in Dentistry

4. Overuse in situations in which patients are not at risk for metastatic infections

5. Treatment of chronic periodontitis that is almost totally amenable to mechanical therapy

6. Administration of antibiotics instead of mechanical therapy for periodontitis

7. Long-term administration in the management of periodontal disease
Inappropriate Antibiotic use in Dentistry

8. Antibiotic therapy instead of incision and drainage

9. Administration to avoid claims of negligence

10. Administration in improper situations, dosage, and duration of therapy
Antibiotics Mechanism of Action

• Most often derived from yeasts and fungi
• Only 3 synthetics: sulfonamides, fluoroquinolones, oxazolidinones
Antibiotics

- ANTIBIOTIC EFFECTIVENESS
- MIC-90
- SERUM CONCENTRATION NEEDED TO INHIBIT 90% OF THE SPECIES OF A MICRO-ORGANISM
- PEAK SERUM LEVEL
- SERUM HALF LIVE (T1/2)
Bacteria – the problem

- > 400 known morphologic and biochemically distinct bacterial groups that colonize in the oral ecological niche

- Mixed gram (+) aerobic and gram (+) and (-) anaerobic polymicrobial bacteria

- Anaerobes normally out # aerobes by 10:1 or 100:1

- Infectious microorganisms are usually native to the host’s normal flora
Oro-facial Infections

- Streptococci viridans
- *Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus, Eubacterium, Veillonella, actinomyces*
- Polymicrobial (2-8 species/infection)
- Precise etiologic microbe identity almost impossible
Otitis Media and Sinusitis

- Otitis media and sinusitis are almost always associated with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae*,

- Infections usually one of the three pathogens

Oro-facial infections

• Associated with viridans group streptococci (VGS), Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus, Eubacterium, Veillonella, and Actinomyces.

• Infection usually associated with 2 to 8 or more pathogens

Probiotics

- Live microorganisms that confer a health benefit to the host
- *Lactobacillus rhamnosus* GG + *Bifidobacterium* strains + *Saccharomyces boulardii*
Beta-lactams

- **Penicillin**
  - Only indicated for minor infections – this includes dental abscesses

- **Ampicillin**
  - Greater activity against gram (-) because it penetrates the gram (-) cell membrane

- Downside
  - Beta-lactamases inactivate
  - Multiple resistant bacterial strains

- **Amoxicillin**
  - Better bioavailability
  - Downside
    - Beta-lactamases inactivate
    - Add Clavulanic acid
    - Multiple resistant bacterial strains
Resistance to Penicillin

1. Inactivation by $\beta$-lactamase

2. Gram (-) permeability barrier that prevents penicillins from entering the cell

3. Confirmation changes in the PBP structure (MRSA)
Penicillin Resistance

β-lactamase breaks a bond in the β-lactam ring of penicillin to disable the molecule. Bacteria with this enzyme can resist the effects of penicillin and other β-lactam antibiotics.
Penicillin Allergy

- Allergic reactions to penicillins common
- Allergic fatalities are far less common.
- Penicillins allergies ranges from 0.7% to 8% (average of 2%)
- Most allergic manifestations are maculopapular or urticarial skin reactions.

• Penicillin most common cause of anaphylactic death in the United States, accounting for 75% of all cases and 400 to 800 annual deaths.

• Penicillin-induced anaphylaxis is most common in adults 20 to 49 years old.

• Estimates of severe penicillin anaphylaxis range from 0.004% to 0.015% of individuals exposures

• Based upon number of exposures, 1 in 1200 to 1 in 2500 penicillin exposures.

• Fatality rate from penicillin anaphylaxis by all routes of administration: 1 in 60,000 patient courses (16 per 1 million),

MULTIPLE ANTIBIOTIC ALLERGY SYNDROME

- Constitute 1% to 4% of all patients who have taken multiple antibiotics.

- Serious adverse drug reactions such as anaphylaxis with antibiotics are rare except for the β-lactams.

MULTIPLE ANTIBIOTIC ALLERGY SYNDROME

- Some difficulties with the health history
- Patients may confuse any adverse drug reaction with “allergy,”
- Rarely are any of these “allergies” confirmed by skin testing
- Often the patient’s history is nebulous

MULTIPLE ANTIBIOTIC ALLERGY SYNDROME

- Management of such patients requires a detailed medical history, including
  - when during the treatment the reaction occurred
  - what infectious disease was being treated
  - what doses of antibiotics were taken and for how long, and, most important
  - what were the signs and symptoms

MULTIPLE ANTIBIOTIC ALLERGY SYNDROME

• Determine the signs and symptoms of an acute IgE-mediated allergic reaction—rash, angioedema, bronchospasm, and syncope

• Time between drug ingestion or administration and onset of symptoms

  • If the onset of signs and symptoms occurred within 1 hour of ingestion or administration, it was likely an immediate allergic reaction

  • Possible skin test (reliable only for β-lactams) is indicated and a specific management plan.

• Comorbid conditions that may increase the incidence of allergy in general are atopic disease (asthma, eczema), chronic urticaria, nonsteroidal anti-inflammatory drug (NSAID) intolerance, immunosuppression, human immunodeficiency virus (HIV) positivity, and a history of multiple antibiotic use.

Cephalosporins

• Broader spectrum than β-lactams
• More stable to β-lactamases
• 1st generation (cephalexin): gram (+) activity and anaerobes sensitive
• Later generations (Cefaclor, Cefotaximer, Cefepine): improved gram(-) activity
• Less expensive than Augmentin®
• Less bacterial resistance
Cephalosporins

- Most effective treatment for sinusitis
- Cellulitis + other soft tissue infections
Tetracyclines

- Broad spectrum
- Bacteriostatic for many gram (+) and (-) aerobes and anaerobes
- Bound to developing teeth and bones
  - Inhibits bone growth
- Used to treat Helicobacter pylori (HP) in
TETRACYCLINES

- OPPORTUNISTIC CANDIDA INFECTIONS
- SUN SENSITIVITY
Tetracyclines

- Doxycycline (Vibramycin)
  - MOA: inhibit protein synthesis by preventing aminoacyl transfer RNA from entering the acceptor sites on the ribosome
  - Dose: 100 mg 1 or 2 a day for 14 days
  - Contraindications:
    - Food
    - Pregnancy - Category D
  - Adverse events: GI
  - Drug interactions: anti-epileptics
Macrolides

- Erythromycin
  - Gram (+) and Gram (-) activity
  - Low doses bacteriostatic
  - High doses bactericidal
  - Suitable alternative for penicillin allergic pt.
What’s Good

• Property of macrolides and highly fat-soluble tetracyclines and clindamycin is selective uptake by phagocytic cells and fibroblasts, which function as repository drug depots and as a drug delivery system to areas of inflammation and infection

• Phagocytic and fibroblasts cells concentrate the macrolides and then transport them to areas of tissue pathology where they are released for their anti-infective and anti-inflammatory properties

• Tissue concentrations of azithromycin may reach 100 to 1000 times that of blood and persist long after blood levels have declined because of their significant postantibiotic effects

• The tissue concentration of azithromycin may exceed the microorganism’s MIC for 2 to 10 days, and the elimination 1/2 life in abscesses is 4 days

Macrolides

- Drug interactions (inhibits P450 enzymes in liver)
  - Increases serum concentrations
    - Theophylline, warfarin, cyclosporine, methylprednisolone, digoxin
  - Decreases activity
    - Plavix
Macrolides

- Clarithromycin (Biaxin®)
  - Greater acid stability and oral absorption
  - Twice day dosing
  - Major metabolite (14-hydroxyclarithromycin) has antibacterial activity also
  - Decreased GI intolerance
  - Downside
    - Expensive
    - CLARICOR study 500 mg daily for 14 days ↑ mortality in pts. with stable coronary artery disease
Macrolides

• Azithromycin

• Less activity against staphylococci and streptococci

• Greater activity against HP

• Penetrates tissues better (exceeding serum concentration by 10 – 100 fold)

• Slowly released from tissues with a tissue half-life of 2 to 4 days and an elimination half-life of 3 days.
• Most attractive aspect of azithromycin is a 15-member lactone ring as opposed to the shoddy 14-member lactone ring of erythromycin and clarithromycin!

• Why?
  • The 15 member ring does not inhibit P450 enzyme activity and therefore azithromycin is free of the multiple drug interactions!!!
Macrolide Adverse Effects

- Serious adverse reaction associated with macrolides, particularly erythromycin, is potentially severe epigastric pain resulting from stimulation of the gastric smooth muscle motilin receptor.

- Motilin is a regulatory peptide of the gastrointestinal tract that stimulates enzyme secretions by the stomach and pancreas and induces strong phasic contractions of the stomach.

- Most significant agonists of the motilin receptor are the 14-membered macrolides (erythromycin); azithromycin and clarithromycin are lesser stimulants.

Azithromycin

- FDA warning Heart Risks March 2013
- May cause prolonged cardiac repolarization and QT interval
- High risk patients: history of existing QT-interval prolongation torsade de pointes, congenital long QT syndrome, uncompensated heart failure, hypokalemia, hypomagnesemia or significant bradycardia
Clindamycin

- Activity against streptococci staphylococci, pneumococci
- Enterococci and gram(-) aerobes resistant (does not penetrate gram(-) outer membrane) (Clostridium difficile is resistant)
- Well absorbed orally – food does not reduce absorption significantly
## Pseudomembranous Colitis

- 280,000 patients
- Rate per 100,000 population

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicilllin</td>
<td>1.6</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>2.9</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2.6</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0</td>
</tr>
</tbody>
</table>
Fluoroquinolones

- Excellent Gram (-) aerobes and little gram(+) activity
- Newer agents more gram (+) activity
- Well absorbed
- Wide volume of distribution
- Since most dental infections have high concentrations of anaerobes – and most fluoroquinolones demonstrate little or no activity against anaerobes – rarely a good choice
FLUOROQUINOLONES

• CIPROFLOXACIN (CIPRO)

• INTERFER WITH DNA REPLICATION BY INHIBITING DNA GYRASE

• GOOD STAPH AND GRAM -

• POOR STREP AND ANAEROBES

• NO INDICATIONS IN DENTISTRY

• EXPENSIVE
Dr. Rutkowski,

My name is Marcus Palermo. I am an endodontist practicing in Scottsdale, AZ and currently enrolled in the Loma Linda Maxi Course. I am writing to ask about the use of Ciprofloxacin and its side effects. I have a patient who has an abscess that hasn’t cleared up with endodontic retreatment and prior to attempting apical surgery I elected to attempt an antibiotic protocol that I have never used.

I had a friend tell me that they have used it with some success in the past, so I gave it a try. Basically, I placed the patient on 250mg Cipro bid for 3 days and combined it with Metronidazole 250mg bid as well for 3 days. The patient is a 33 year old healthy male. He is not taking any medications and has only an allergy to sulfa medications. He took the medication without consequence for the 3 days. On day 5 he began to notice some joint pain, especially in his knees. He is a bright fellow (bachelor’s in astrophysics) and did some research over the weekend and read about ligament damage as a side effect from Cipro. He has started taking magnesium supplements and glucosamine as a prophylactic measure.

He contacted me and informed me of his condition and noted that he has some discomfort on waking in the joints and it progressively gets worse as the day goes on. I advised him to take 400mg ibuprofen q6h prn pain and told him that the supplements may help and they certainly won’t hurt. He has researched several forums and read many posts about similar side effects and that they are nearly impossible to resolve and that they can get worse or recur up to 6 months post-treatment. He has asked me what to do and I advised him that I would have to do some of my own research and consult with colleagues (hence this message) and I would get back to him. He has had the pain for about 5 days and it is not getting any worse, but it also is not any better.

I am embarrassed that I used this regimen without consulting further for possible side-effects and management of the sequellae from taking Cipro. Now, I am just trying to understand what has happened and what I might tell my patient that could help him recover quickly. Please share any advice you might have regarding the joint tenderness associated with Cipro.

Thank you for your time!

Sincerely,

James L. Rutkowski, D.M.D., Ph.D.
Hello Marcus, Thanks for your patience on this. Attached is an article that explains the collagen breakdown that seems to be the cause of the tendonitis. A second article attached described treatment with the anti-inflammatory medication (100 mg flurbiprofen daily) and a rehabilitation program. In 15 days after stopping ciprofloxacin treatment, his symptoms gradually improved. On the 35th day, his symptoms disappeared totally. I think any NSAID would have done the job. Hopefully this will help you and the patient. It was great communicating with you on this interesting case. I would like to know how it resolves as I will most likely include this little know side effect in my pharmacology lecture on antibiotics now. Please email back that you received this and were able to open the attachments. Best,
Jim

James L. Rutkowski, D.M.D., Ph.D.
Metronidazole

- Great anaerobic activity
- Well absorbed
- Widely distributed
- Anaerobic bacteria reduce the nitro group to give the antimicrobial activity
- May give a metallic taste
- Do not consume alcohol – re. disulfiram-like reaction
• Chance observation that the symptoms of acute necrotizing ulcerative gingivitis were relieved in a woman receiving metronidazole for the treatment of vaginal trichomoniasis stimulated research on the drug’s antibacterial effects, culminating in its approval in 1981 for the treatment of anaerobic bacterial infections.
Metronidazole

- Effective against gram-negative anaerobic pathogens responsible for acute orofacial infections and chronic periodontitis

- Combination of metronidazole with a β-lactam antibiotic for oral infections may be indicated for serious acute orofacial infections and in the management of aggressive periodontitis.
Questions

• What are the empiric antibiotics of choice for odontogenic infections (OI)

• How Long should the treatment course last?

- Analysis - relevant articles
  - 40 review articles - 3 review articles found to meet criteria
  - Potentially relevant articles
  - 1003 potential articles
  - 772 articles for antibiotic treatment in OI
  - 228 articles for antibiotic sensitivity in OI
  - 3 trials of antibiotic treatment course duration
Articles used

- 23 clinical trials of antibiotic treatments in OI
- 18 laboratory studies of antibiotic sensitivity from OI
- 3 trials of antibiotic treatment course duration
Clinical Trials of Antibiotics
8 trials 488 patients

- Antibiotics examined
  - Penicillin VK, Penicillin G-IM,
  - Amoxicillin/Clavulanate, Ampicillin, Amoxicillin, Clindamycin, Lincoycin, Cephalexin, Metronidazole, Ornidazole, Moxifloxacin
Which Antibiotic?

• No statistically significant difference in clinical cure rates at day 7

• Randomized, non-blinded trial compared amoxicillin, cephalexin, and surgery alone

• Amoxicillin - 4.5 days, cephalexin 4.7 days, surgery alone 6.2 days
Laboratory Studies
4 publications - 280 patients

- Bacterial strains $3.0 \pm 1.3$ (2.4 - 5.5)
- Penicillin, ampicillin, beta-lactam/beta-lactamaze inhibitor combination, clindamycin, fluoroquinolone, doxycycline, minocycline, erythromycin, cephalosporins, imipenem, metronidazole, gentamicin
Which Antibiotic

- No one antibiotic is likely to be effective in vitro against all strains of all species.
- The combination of penicillin and metronidazole would have been effective against all strains of all species, consistent with the clinical strategy of using 1 antibiotic highly effective against the oral Streptococci and another for the oral anaerobes.
How Long?
2 studies 101 patients

• Compared short (1-3 days) with long (5-7 days) courses of therapy

• Antibiotics: penicillin and amoxicillin

• Surgery in both groups
How Long

- No clinically significant cure at 7 days when either a 1-3 day or a 5-7 day therapy when used in combination with surgery

- More rapid decrease of welling with amoxicillin vs penicillin
Dental Infection

Acute - rapid growth < 3 days

Pen VK 1000 mg initially, then 500 mg q 6 h
or
Amoxicillin 1000 mg initially, then 500 mg q 8 h
or
Cephalexin 1000 mg initially, then 500 mg q 6 h
(all of the above for 7 to 10 days or longer)

Penicillin allergy:
Clindamycin 300 mg initially, then 150 mg q 6 h or
Cephalexin (for 7 to 10 days) or
Azithromycin (5 days)

Chronic > 3 days
Choose one

Think Anaerobes: Add
Metronidazole 500 mg 1st time then 250 q 8 hr
for 14 days

Clindamycin 300 mg initially, then 150 mg q 6 h for 7 to 10 days
Therapeutic rationale

- Empirical therapy
  - Early intervention will improve the outcome
  - Accepted by placebo-controlled, double-blind prospective clinical trials
  - Base on scientific knowledge & clinical experience
Therapeutic regimen

• Step 1. Penicillin-like antibiotic meets criteria for activity against anaerobic gram (-) and aerobic gram(+) bacteria

• Amoxicillin logical 1st choice, with exception of anaerobes possessing beta-lactamase activity – then consider Augmentin® - BUT very expensive -- so cephalexin (demonstrates greater stability than penicillins and less expensive than Augmentin®)
**Therapeutic**

- Step 1. summary:

  - Cephalexin 1000 mg initially, followed by 500 mg every 6 hours for a total of 7 to 10 days.
Therapeutic regimen

• Step 2. If the beta-lactam antibiotic (cephalexin) fails to bring resolution after 48 to 72 hrs. then consider improving anaerobe coverage

A. Add metronidazole 500 mg initially followed by 250 mg every 8 hours for 7 to 10 days.

   OR

B. D/C cephalexin and begin clindamycin 300 mg initially follow by 150 mg every 6 hours for 7 to 10 day.
BACKGROUND/AIM: The most common cause of acute dental infections are oral streptococci and anaerobe bacteria. Acute dentoalveolar infections are usually treated surgically in combination with antibiotics. Empirical therapy in such infections usually requires the use of penicillin-based antibiotics. The aim of this study was to investigate the clinical efficiency of amoxicillin and cefalexin in the empirical treatment of acute odontogenic abscess and to assess the antimicrobial susceptibility of the isolated bacteria in early phases of its development.
RESULTS: The infection signs and symptoms lasted on the average 4.47 days, 4.67 days, and 6.17 days in the amoxicillin, cephalexin, and surgically only treated group, respectively. A total of 111 bacterial strains were isolated from 90 patients. Mostly, the bacteria were Gram-positive facultative anaerobs (81.1%). The most common bacteria isolated were Viridans streptococci (68/111). Antibiotic susceptibility of isolated bacteria to amoxicillin was 76.6% and cefalexin 89.2%.
• **CONCLUSION:** Empirical, peroral use of amoxicillin or cefalexin after surgical treatment in early phase of development of dentoalveolar abscess significantly reduced the time of clinical symptoms duration in the acute odontogenic infections in comparison to surgical treatment only. Bacterial strains isolated in early stages of dentoalveolar abscess showed high sensitivity to amoxicillin and cefalexin.
THERAPEUTIC REGIMEN

- Penicillin 500-1000 mg QID
- Cephalexin 500-1000 mg QID
- Erythromycin 250-500 mg QID
- Amoxicillin 500-1000 mg TID
- For 2-3 days if better continue
  - If not better then:
THERAPEUTIC REGIMEN

• Add metronidazole
  • 500 mg stat then 250 mg TID
• Switch to clindamycin
  • 150-300 mg QID
• If not successful then:
  • Culture & sensitivity
  • Always consider incise & drain and moist heat
SURGICAL PROPHYLAXIS

• Adequate serum level within 2 hrs. of incision

• Serum level should not Best continued for more than 24 hours

• Prolonged
  • Growth of resistant organisms
SURGICAL PROPHYLAXIS

- Use bacterial endocarditis prophylaxis regimen
  - Plus 1 or 2 additional doses
  - Oral amoxicillin, cephalexin, penicillin VK, clindamycin
  - IV cefazolin then oral cephalexin
MEDICAL PROPHYLAXIS

- Compromised immune function
- Poorly controlled insulin dependent diabetic
  - Renal failure with dialysis
  - Evidence of significant malnutrition or alcoholism
- Symptomatic HIV
- Immunosuppressant drugs
- Radiation of head and neck
Inflammatory arthropathies including rheumatoid arthritis and systemic lupus erythematosus

First 2 years following joint placement

Previous prosthetic joint infection
Infective Endocarditis (IE)

Bacteria in blood stream

Matrix molecules & platelets at sites of endocardial cell damage

Substantial Morbidity & Mortality
IE

- Nonbacterial thrombotic endocarditis (NBTE) on surface of host’s cardiac valve or elsewhere that endothelial damage has occurred

- Bacteria from bacteremia adheres
  - *Streptococci viridans* – *Fim A*
  - Staphylococci - biofilm
  - Enterococci

- Vegetation – 90% bacteria in mature vegetations are metabolically inactive – not actively growing – less responsive to antibiotics
Cardiac conditions related with the greatest risk of adverse outcome from IE for which prophylaxis with dental procedures is recommended

<table>
<thead>
<tr>
<th>Prophylactic Cardiac Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic cardiac valve</td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
</tr>
<tr>
<td>Congenital heart disease (CHD)*</td>
</tr>
<tr>
<td>Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
</tr>
<tr>
<td>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure**</td>
</tr>
<tr>
<td>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac valvuopathy</td>
</tr>
</tbody>
</table>

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD

**Prophylaxis is recommended because endothelialization of prosthetic material occurs within six months after the procedure
IE regimen: Single dose 30 to 60 minutes before procedure:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Agent</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2 gms</td>
<td>50 mg per kg</td>
</tr>
<tr>
<td>Unable to take oral meds</td>
<td>Ampicillin OR Cefazolin or Ceftriaxone</td>
<td>2 gms IM or IV 1 gm IM or IV</td>
<td>50 mg/kg IM or IV 50 mg/kg IM or IV</td>
</tr>
<tr>
<td>Allergic to Pencillins or Ampicillin Oral</td>
<td>Cephalexin OR Clindamycin OR Azithromycin</td>
<td>2 gms. 600 mg 500 mg</td>
<td>50 mg/kg 20 mg/kg 15 mg/kg</td>
</tr>
<tr>
<td>Allergic to Penicillins or Ampicillin and Unable to take oral meds</td>
<td>Cefazolin or Ceftriaxone OR Clindamycin</td>
<td>1 gm IM or IV 600 mg IM or IV</td>
<td>50 mg/kg 20 mg/kg</td>
</tr>
</tbody>
</table>
Metronidazole with Lithium

- Lithium is a monavalent cation
- Lithium is indicated for bipolar
- Met. interferes with renal excretion of lithium
- Close supervision with lithium
- Therapeutic Index
Blood Levels

- 0.8 to 1.5 mEq/L during acute manic attack
- 0.6 to 1.2 mEq/L for maintenance therapy
- Toxicity occurs at 1.5 to 2.0 mEq/L
- Above 2.5 mEq/L - life threatening
Metronidazole with Lithium

- Three cases of metronidazole for one week 500-1000 mg. per day leading to toxicity (JAMA 1987 and Int. Drug Ther. News 1982)
- Avoid metronidazole with lithium patients
- Significance rating is 1
ANTIBIOTICS + ORAL CONTRACEPTIVES

- Rifampin (TB) only confirmed
- Anecdotal reports
- OC failure 0.5 - 1.0% (Teens 8%)
- Enterohepatic recycling
- Studies do not substantiate this
- MILLER et al HANDOUT
Oral Contraceptives

- Semisynthetic estrogens
- Semisynthetic progesterones
- Estrogens block release of FSH and LH
- Progesterones enhance viscosity of cervical fluid
Oral Contraceptives

- Typical failure rate 3% - Teens 8%
- Most likely due to failure to take pill
Rifampin Interaction

- Tx: TB
- 76% of interactions
- Decrease in blood levels of BC Pills
- Inducer of liver Cytochrome P-450
Ref.

Hersh, E., JADA Feb. 1999
Antibiotics and Oral Contraceptives

- 1975 - 3 cases Ampicillin
- 1980 - 1 report Tetracycline
- 1982 - 13 cases Ampicillin, Penicillin, Tetracycline
- 1986 - I.M. Penicillin
“Unfortunately, many antibiotics commonly used in dentistry interfere with the action of oral contraceptives, resulting in unexpected pregnancies. Failure to inform a patient using oral contraceptives during antibiotic therapy resulting in a birth could leave the dentist responsible for damages—including child support payments.”

JADA, 1991
Ref. Hersh, E., JADA Feb. 1999
JADA Statement

• “The failure of oral contraceptives in women simultaneously ingesting antibiotics may indicate background noise— that is, the normal failure rate of these drugs or a relatively rare interaction that cannot be detected by clinical trials”

JADA, February 1999
“Wrongful Life”

- GYN and OS - Plaintiff lost
  - her experts cited review articles with no data
  - her experts failed to show a scientifically validated interaction existed
- CA law - physicians do not have to discuss risks of a very low incidence
  - her experts failed to prove that she became pregnant when she was taking penicillin
Antibiotics and Oral Contraceptives

- Significance rating 4 (except Rifampin)
Erythromycin, Clarithromycin or Tetracyclines with Digoxin

- Digoxin has low therapeutic index
- 10% of population harbors enteric bacteria that inactivates digoxin
  - > average dose - antibiotic kills off bacteria
    ⇒ very high levels of digoxin

Erythromycin, Clarithromycin or Tetracyclines with Digoxin

- Erythromycin ⇒ problems in less than three days
- Tetracycline ⇒ 30% rise in digoxin levels
- Significance rating 1
Metronidazole with Alcohol

- Metronidazole (like Antabuse) inhibits activity of acetaldehyde dehydrogenase
- ⇒ get accumulation of acetaldehyde when taken with alcohol
- unpleasant reaction
Metronidazole with Alcohol

- No alcohol for at least 3 days after Metronidazole therapy
- Significance rating 2
Tetracyclines/Broad Spectrum Antibiotics with Oral Anticoagulants

- Coumadin has a low therapeutic index
- Antagonist of Vitamin K dependent clotting factors
- Tetracycline, Amoxicillin and Ampicillin
  - reduce endogenous Vit. K levels
  - enhance the effects of oral anticoagulants by decimating normal gut flora that produce Vit. K
Tetracyclines/Broad Spectrum Antibiotics with Oral Anticoagulants

- Reaction if unpredictable
- Concern in patients with low Vitamin K diet
- Normal Vitamin K intake $\Rightarrow$ no problem
- Significance rating 4
Erythromycin, Clarithromycin or Metronidazole with Oral Anticoagulants

- Can get marked increase in Warfarin levels
Erythromycin, Clarithromycin or Metronidazole with Oral Anticoagulants

• Erythromycin etc. - 30% reduction in clearance of Warfarin
• Marked increase in anticoagulant activity
• Block the cytochrome P-450 \( \Rightarrow \) interferes with Warfarin metabolism
• Significance rating 1
ANTICOAGULANT CLASSES

- **INHIBITORS OF CLOTTING FACTOR SYNTHESIS**
  - Warfarin (Coumadin®)
  - Rivaroxaban (Xarelto®)

- **INHIBITORS OF THROMBIN**
  - Heparin, Lepirudin (Refludan™)
  - Dabigatran Etexilate Mesylate (Pradaxa™)

- **PREVENTION OF PLATELET AGGREGATION**
  - ASA
  - Ticlopidine (Ticlid™)
  - Clopidogrel (Plavix™)
  - Tirofiban (Aggrastat™)
  - Eptifibatide (Integrilin™)
  - Prasugrel (Effient™)
  - Ticagrelol (Brilinta®)
ANTICOAGULANTS

• WARFARIN (COUMADIN)
  – ACTS IN LIVER BY INHIBITING REDUCTION OF VIT. K TO A FORM NEEDED FOR SYNTHESIS OF FACTORS VII, IX, X, AND PROTHROMBIN

• HEPARIN
  – POTENTIATES THE ANTICOAGULANT ACTIVITY OF ENDOGENOUS ANTITHROMBIN III
COUMADIN®

- EFFECT IN 24 HRS.

- PEAK 3 – 4 DAYS

- MAY CAUSE SERIOUS HEMORRHAGE
  - ANTIDOTE – VIT. K

- REQUIRES 12 – 24 HRS.

- MAY REQUIRE TRANSFUSION
Warfarin

- Outpatient Rx’s 2004 - 31 million
- Ranked 1st in 2003 and 2004 for drug related deaths due to “adverse effects” in therapeutic use
- 10 to 16% of patients will have a major bleed at some point
- No longer acceptable to D/C warfarin routinely!!!
COUMADIN®

• Monitor with INR (International normalized ratio)

  – Standardizes the various laboratories thromboplastins (human or rabbit)
Recommended range for oral anticoagulant therapy:

INR target range 2.0 to 3.0
- Prophylaxis/treatment of venous thrombosis
- Treatment of pulmonary embolism
- Prevention of systemic embolism
- Recurrent systemic embolism
- Acute myocardial infection
- Valvular heart disease
- Valvular replacement with tissue
- Atrial fibrillation

INR target range 2.5 to 3.5
- Mechanical replacement heart valves (High risk)
INTERNATIONAL NORMALIZED RATIO (INR)

- INR < 2.0 out of therapeutic range (poorly managed – needs adjustment)

- INR 2.0 → 4.0 ok to do surgery with local measures

- INR > 4.0 out of therapeutic range – (warfarin dosage needs adjustment)
Warfarin (Coumadin®)

Good
- Continue warfarin therapy
- Hemorrhagic disorders
- Correct INR

Bad
- D/C warfarin therapy
- Malpractice
- Cerebrovascular complications
- Thrombosis formation
Should warfarin be discontinued before a dental extraction? 
A decision-tree analysis

Ben Balevi, BEng, DDS, DipEBHC (Oxford), MSc, Vancouver, Canada

Objective. The aim of this study was to determine if warfarin should be withdrawn before a single tooth extraction on a patient with a prosthetic heart valve.

Study design. A quantitative decision tree was constructed to assess the expected utility values of 2 typical strategies to manage the dental extraction on a patient currently medicated with warfarin. Probabilities and utilities for a cardiovascular accident and major bleeding from a dental extraction were taken from the literature.

Results. The decision slightly favors withholding warfarin: generating an optimal expected utility value of 0.976 utile. This was only 0.02 utile higher than the alternative option of continuing warfarin for a dental extraction.

Conclusion. The decision to withhold or continue warfarin before a dental extraction depends more on the relative risk of a major bleeding between the 2 medical management strategies than on the consequences of a cardiovascular accident. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:691-697)
CONCLUSION

The decision to withhold or continue warfarin before a dental extraction depends more on the RR of major bleeding between the two medical management strategies than on the consequences of a CVA. For the minimally invasive single tooth extraction, not disrupting the patient’s warfarin protocol and using local adjunctive means of hemostasis is defensible. However, in cases that are significantly invasive and/or involve multiple dental extractions, withholding warfarin may be indicated, because of the risk and thus the negative consequences of major bleeding as perceived by the patient.
Also, I have finished reviewing the OOOOE article on warfarin. Bottom line, there is no statistical weight whatsoever behind the article's recommendation to withhold warfarin. The EUV estimates are separated by only 0.02, and all of the probabilities used to estimate the two EUV values are themselves estimates (from other literature, no less).

This article is in no way a breakthrough or landmark. Would it be okay for me to call you and discuss in more detail my critique of the article? I can call most any time/day this week or next; just let me know.

I hope your new year has gotten off to a great start!
DRUGS WITH THE POTENTIAL TO AFFECT ANTICOAGULANT THERAPY.

### MEDICATIONS THAT POTENTIATE THE EFFECT OF COUMARIN
- Acetaminophen
- Cephalosporins
- Chloral hydrate
- Corticosteroids
- Diflunisal
- Erythromycin
- Fluconazole
- Ketoconazole
- Metronidazole
- Nonsteroidal anti-inflammatory drugs
- Penicillins
- Propoxyphene
- Salicylates
- Tetracyclines

### MEDICATIONS THAT OPPOSE THE EFFECT OF COUMARIN
- Ascorbic acid
- Barbiturates
- Dicloxacillin sodium
- Nafcillin

Ref. Herman W., et. al., Current Perspectives On Dental Patients Receiving Coumarin Anticoagulant Therapy, JADA March 1997
TAKE-HOME MESSAGE

• MUST HAVE A RECENT INR (WITHIN 30 DAYS IF NO CHANGES IN MEDS)

• IF ANY MED OR DOSAGE CHANGES – THEN MUST REPEAT INR

• BEST IF SAME-DAY FOR MAJOR PROCEDURES!!!
dabigatran (Pradaxa®)

Boehringer Ingelheim

• For prevention of stroke and systemic embolism (blood clots) in patients with atrial fibrillation

• first replacement for warfarin (Coumadin®) since Coumadin was approved in 1954.
Intrinsic activation

Surface contact
- Factor XII
- Factor XI
- Factor VIII
- Factor IXa
- Factor X

Extrinsic activation

Vessel injury
- Factor VII

Factor XIIa

Prothrombin

Factor Xa

Rivaroxaban

Dabigatran etexilate

Thrombin

“Serine protease”

Fibrinogen

Fibrin
dabigatran (Pradaxa®) 

anticoagulant

• acts by inhibiting thrombin, an enzyme in the blood that is involved in blood clotting

• thrombin (serine protease) enables the conversion of fibrinogen to fibrin during the coagulation cascade, its prevention prevents the development of a thrombus.

• recommended dose is a 150 mg capsule taken orally

• Warfarin therapy requires patients to undergo periodic monitoring with blood tests
  • INR monitoring not necessary for dabigatran.
dabigatran (Pradaxa®)

- Measure of Effect
  - At therapeutic doses prolongs the activated partial thromboplastin time (aPTT)
  - Oral dose of 150 mg twice daily, the median peak aPTT is approximately twice that of control values
  - Twelve hours after the last dose, the median aPTT is 1.5x control
  - INR test is relatively insensitive to the activity of dabigatran and may not be elevated in patients on dabigatran.
Dabigatran (Pradaxa®)

• Absorption and Metabolism
  • After swallowing a dabigatran (Pradaxa) capsule, peak blood level occurs in 1 hour. The half-life is 12 to 17 hours.
  • not metabolized by CYP enzymes
  • After oral administration, dabigatran etexilate is converted to dabigatran through esterase-catalyzed hydrolysis of the molecule in plasma
  • Dabigatran is not a substrate, nor inhibitor, nor inducer of CYP 450 enzymes
Dabigatran and Risk of Bleeding

- ↑ risk of bleeding and can cause significant, and sometimes fatal, bleeding
  - Drugs that can increase the risk of bleeding include antiplatelet agents and chronic use of NSAIDs

- RE-LY trial, life-threatening bleeding occurred at an annualized rate of 1.5% for Pradaxa 150 mg and 1.8% for warfarin.

- Discontinuing Pradaxa for surgery places the patient at an ↑ risk of stroke
  - If anticoagulation must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

- Dental patients who may have a high risk of bleeding if taking Pradaxa include those over 75 years of age, or are taking aspirin, or long term NSAIDs, or clopidogrel (Plavix®) or prasugrel (Effient®).

Rivaroxaban (Xarelto®)

- Mechanism: Factor Xa inhibitor
  
  In coagulation factor X $\rightarrow$ Xa (produces fibrin)
Rivaroxaban (Xarelto®)

- Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in pts undergoing knee or hip replacement surgery
- 10 mg once daily
- 5 -6% pts have “a bleeding event”
Rivaroxaban (Xarelto®)

- Measurement of Effect
  - Prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT)
    - Predictive treatment values not established
  - No data on INR use
  - Hip replacement - 35 days
  - Knee replacement - 12 days
Rivaroxaban (Xarelto®)

- Dental considerations
  - ↑ bleeding occurs with 10mg/day
  - Consult
  - No reports of interactions with amoxicill, cephalexin, cefazolin, ampicillin, & clindamycin
Rivaroxaban (Xarelto®)

• Drug interactions
  
  – Inhibitors of CYP3A4
    • Ketocanazole (antifungal)
    • Clarithromycin (Biaxin®)
    • Erythromycin
  
  – NSAIDS
THROMBOGENESIS

• PLATELET AGGREGATION

• COAGULATION
ARTERIAL COAGULATION

– CASCADE TO FIBRIN STRANDS

• ARTERIES

  – PLATELETS ADHERE TO DAMAGED VESSEL WALLS
  – AGGREGATE
  – CORE FOR FIBRIN STRANDS
  – OCCLUDE ARTERIAL FLOW
  – ISCHEMIA OF LOCAL TISSUES
VENOUS THROMBOSIS

- FIBRIN STRANDS
  - EMBOLIZE GREAT DISTANCES
  - LODGE IN PULMONARY ARTERIES
THROMBOGENESIS

• LOCALIZED RESPONSE

  – INITIATED BY SUBSTANCES RELEASED FROM PLATELETS AND ENDOTHELium

  – LIMITED BY LOCALIZED ANTICOAGULANT MECHANISMS

• ANTITHROMBIN II
ANTIPLATELET DRUG

• ASPIRIN
  - TX: PREVENTION OF MI & THROMBOTIC STROKE
  - 81 mg/day
  - LITTLE RISK FOR DENTAL SURGERY
ANTIPLATELET DRUG

• DIPYRIDAMOLE (PERSANTINE)
  – PREVENTS PLATELET ADHESION TO ENDOTHELIAL SURFACES
  – MIXED WITH ASA
    • ENHANCES ANTITHROMBOBOTIC ON ARTIFICIAL SURFACES
      – VALVULAR & CARDIAC PROSTHESES
  – DIALATES CORONARY ARTERIES
PLAVIX® - CLOPIDOGREL

• BLOCKS THE ADP RECEPTOR WHICH PREVENTS THE BINDING OF FIBRINOGEN TO THAT SITE

• DOES NOT ALTER THE RECEPTOR

• REDUCES # OF FUNCTIONAL ADP RECEPTORS
PLAVIX® - CLOPIDOGREL

- MONITOR WITH PLATELET AGGREGATION
- INITIAL 2 TO 4 WEEKS MAY CAUSE THROMBOCYTOPENIA – CHECK PLATELETS
- RARELY NECESSARY TO D/C
- SURGERY IF MULTIPLE SITES OR EXTENSIVE? – get consultation
  - DISCONTINUE 7 DAYS PRIOR TO PROCEDURE (RARELY NECESSARY!)
• 30% of population has a genetic variant in liver metabolizing enzymes that affect efficacy of clopidogrel - no effect at all

  – CYP2C19 converts clopidogrel to an active metabolite.

  – Genes which encode and express liver enzymes responsible for metabolism exist in several polymorphic states (CYP2C19 has 4 variants with reduced function)

  – Relative reduction of 32% in active metabolite

  – 53% higher risk for primary efficacy outcome of death from cardiovascular causes, MI, stroke

  – Stent thrombosis in carriers 3 X that of non-carriers

Prasugrel (Effient™)

- Antiplatelet agent and aggregation inhibitor

  - For ↓ thrombotic cardiovascular events (stent thrombosis)

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel Non-fatal subsequent heart attacks</th>
<th>Prasugrel Non-fatal subsequent heart attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths and strokes</td>
<td>9.1%</td>
<td>7%</td>
</tr>
<tr>
<td>Deaths and strokes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths and strokes</td>
<td>Deaths and strokes equal</td>
<td>Deaths and strokes equal</td>
</tr>
<tr>
<td>Deaths and strokes</td>
<td>Risk of significant fatal bleeding</td>
<td>Risk of significant fatal bleeding</td>
</tr>
<tr>
<td>Deaths and strokes</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Prasugrel (Effient™)

• Pro-drug

• Irreversibly blocks P2Y12 component of adenosine diphosphate (ADP) receptors on platelets for their lifespan
  
  – ↓ platelet activation and platelet aggregation

  – Normal platelet activity does not return (new platelets in 5 to 9 days after D/C

  – Loading dose 60 mg followed by maintenance dose of 10 mg daily.

  – Should take with ASA 75 to 325 mg daily
Prasugrel (Effient™)

- Genetic variants in liver metabolizing enzymes do not affect efficacy
  - Undergoes rapid intestinal and serum metabolism via esterase-mediated hydrolysis to a thiolactone (inactive metabolite), which is then converted, via CYP3A4 & CYP2B6 enzyme oxidation, to the active metabolite designated as R-138727.
Ticagrelor (Brilinta®)

- Reduce rate of thrombotic cardiovascular events in pts with acute coronary syndrome (ACS): unstable angina, non-ST elevation MI, ST elevation MI
- More effective than clopidogrel
Ticagrelor (Brilinta®)

- Drug interactions
  - Inhibitors of CYP3A4
  - Ketocanazole
  - Itaconazole
  - Voriconazole
  - Clarithromycin (Biaxin®)
  - Erythromycin

- NSAIDs
Ticagrelor (Brilinta®)

• Mechanism: An active, reversible platelet inhibitor

• CYP3A4 converts ticagrelor to another active reversible platelet inhibitor - which is the major active metabolite

• Act at the ADP-receptor

• Loading dose 180 mg then 90 mg BID
  
  – Give with loading dose ASA 325 mg then 75 - 100 mg. Daily

  – ASA doses above 100 mg/day reduce effectiveness of ticagrelor and should be avoided
Ticagrelor (Brilinta®)

- Dental considerations
- Do NOT D/C without consultation
- Expect bleeding and echymosis
- Pts often have SOB
- No coagulation parameters suggested
Bisphosphonates

• 1st generation (no nitrogen)
  – Etidronate (Didronel™)

• 2nd generation - 10 to 100 X more potent than 1st gen. (nitrogen)
  – Alendronate (Fosamax™)
  – Pamidronate (Aredia™)
  – Ibandronate (Boniva™)

• 3rd generation 10,000 X more potent then 1st gen. (nitrogen with a heterocyclic ring)
  – Zoledronic acid (Zometa™)
  – Risedronate (Actonel™)
Bisphosphonates

- Analogs of pyrophosphate (P-O-P)
- Oxygen is replaced by a carbon
- Concentrate in bone
  - Long $\frac{1}{2}$ life
- Most effective inhibitors of bone resorption
Bisphosphonate: Mechanism of Action

- Capable of chelating $\text{Ca}^{2+}$ - thus strong affinity for remodeling bone
- Prevent hydroxyapatite dissolution (all)
- Anti-resorptive activity also includes
  - Osteoclast apoptosis (1st generation)
  - Inhibition of components of the cholesterol biosynthetic pathway (2nd & 3rd generation)
Bisphosphononate: Mechanism of Action

• Nitrogen containing BPs are incorporated into the osteoclasts

  – Inhibit farnesyl diphosphate synthase (enzyme involved in cholesterol synthesis)

• Leads to ↓ geranylgeranyl diphosphate

  – Protein that is involved in attachment of other proteins and molecules to the cell membrane
vertebral fractures, a 45 percent relative risk reduction was found (relative risk [RR] = 0.55; 95% confidence interval [CI], 0.45 to 0.67).

nonvertebral fractures, 16 percent relative risk reduction was found (RR = 0.84; 95% CI, 0.74 to 0.94).

40 percent relative risk reduction in hip fractures (RR = 0.60; 95% CI, 0.40 to 0.92)

CONCLUSIONS: alendronate clinically and statistically had significant reductions in vertebral, nonvertebral, hip, and wrist fractures were observed for secondary prevention.
New development in bisphosphonate treatment. When and how long should patients take bisphosphonates for osteoporosis?

• Long-term alendronate administration may inhibit normal repair of microdamage arising from severe suppression of bone turnover (SSBT), which, in turn,

• results in accumulation of microdamage. This process would lead to brittle bone and the occurrence of unexpected stress fractures, characteristically at the subtrochanter of femur.
New development in bisphosphonate treatment. When and how long should patients take bisphosphonates for osteoporosis?

• A large-scale study suggests that for more women, discontinuation of alendronate after 5 years for up to 5 more years does not significantly increase fracture risk.

• *Thus, alendronate treatment might be stopped for a while after 5 years to prevent SSBT and subsequent stress fractures.*
Figure 5  Post-operative bone scintigraphy of patient 4 showing increased uptake in the contralateral left femur corresponding to the positions of the stress reactions evidenced on the plain radiograph.
Bisphosphonate Side Effects

Side Effects of Bisphosphonates
BISPHTHOPHONATES AND ALVEOLAR BONE NECROSIS

- Seen with IV bisphosphonate therapy for treatment of osteolytic bone diseases
  - Bisphosphonates are inhibitors of bone resorption via
    - Dissolution of hydroxyapatite
    - Inhibit osteoclast function
Fosamax® (alendronate)

- Reports of bone necrosis with dental surgery?
  - Most likely with bisphosphonates used to treat osteolytic bone lesions such as cancer
  - Not likely with low short term doses of Fosamax® used to prevent osteoporosis
BONJ - Mandible 8/12/09
BONJ - Mandible 10/18/09
Post-Surgery November 4, 2009
April 27, 2011
Have You or Your Loved Ones Taken Fosamax®?

Did You Take Fosamax?

Fosamax Used To Treat Osteoporosis

1-800-940-3365
BISPHOSPHONATES AND ALVEOLAR BONE NECROSIS

• Literature:
  – Editorial Martin Greenberg, DDS
    • Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology Vol 98 #3 Sept. 2004
  – Letter to Editor Cesar Migliorati DDS, MS, PhD
    • OOOE Feb. 2005
  – Aust Dent J. 2003 Dec;48(4);268
BISPHOSPHONATES AND ALVEOLAR BONE NECROSIS

• Literature:
  - J. Clin Oncol. 2003 Nov 15;21(22):4253-4
  Comment
  Ruggiero SL
BISPHOSPHONATES AND ALVEOLAR BONE NECROSIS

• Marx RE, J Oral Maxillofac Surg 63:1567-1575, 2005
• Hellsgrin JW J Oral Maxillofac Surg May 63:1248-9, 2005
BISPHOSPHONATES AND ALVEOLAR BONE NECROSIS

• Tx of bone lesions of multiple myeloma and metastatic bone lesions in pts. with breast and prostate cancer

  – Zoledronate IV (Potent)
  – Pamidronate IV (relatively potent)
  – Alendronate – oral (less potent)
Prevalence of Osteonecrosis of the Jaw in Patients With Oral Bisphosphonate Exposure

Joan C. Lo, MD,* Felice S. O’Ryan, DDS,† Nancy P. Gordon, ScD,‡ Jingrong Yang, MA,§ Rita L. Hui, PharmD, MS,¶ Daniel Martin, DDS,|| Matthew Hutchinson, DDS,# Pbenius V. Latbon,** Gabriela Sanchez,†† Paula Silver,‡‡ Malini Chandra,§§ Carolyn A. McCloskey, MD,¶¶ Judy A. Staffa, PhD,||| Mary Willy, PhD,### Joe V. Selby, MD, MPH,#### and Alan S. Go, MD,####: for the Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators

Conclusions: ONJ occurred in 1 of 952 survey respondents with oral bisphosphonate exposure (minimum prevalence of 1 in 1,537 of the entire mailed cohort). A similar number had select features concerning for ONJ that did not meet the criteria. The results of the present study provide important data on the spectrum of jaw complications among patients with oral bisphosphonate exposure. palatal tori) and 4 occurred in previous extraction sites. An additional 3 patients had mandibular osteomyelitis (2 after extraction and 1 with implant failure) but without exposed bone. Finally, 7 other patients had bone exposure that did not fulfill the criteria for ONJ.
FIGURE 4. Prevalence of ONJ by duration of bisphosphonate (BP) therapy. Error bars represent 95% CIs.
Bisphosphonates & Other Complications

- Severely Suppressed Bone Turnover (SSBT)  
  *Journal of Clinical Endocrinology & Metabolism. 90(3):1294-1301*
  
  - Decreased bone turnover → microfractures

- Alendronate & Atrial Fibrillation. C.I. 0.97 to 2.40; p=0.07  
  
  - Possibly due to release of inflammatory cytokines
This is it!

The Healing Socket And Socket Regeneration

Steiner GG, Francis W, Burrell R, Kallet MP, Steiner DM, Macias R.
Compend Contin Educ Dent. 2008 Mar;29(2):114-6, 118, 120-4

The Healing Socket And Socket Regeneration

• If the first stage of extraction-socket healing is resorption and disposal of necrotic bone, then this would explain why tooth extraction in patients on bisphosphonates occasionally leads to osteonecrosis

• Bisphosphonates prevent osteoclastic undermining and disposal of necrotic bone lining the socket wall

• The inability of the alveolus to dispose of the necrotic bone lining the socket wall could then lead to progressive osteonecrosis
ALENDRONONATE EFFECT OF CELLS

• $[10^{-5}M]$ to $[10^{-11}]$ ↑ cell proliferation

• $[10^{-4}]$ inhibited cell proliferation (inhibition ↑ with time)
  – Ref. Gun-II Im, Biomaterials 25;4105-4115, 2004

  – Bone concentration (vol. 3.63L)
    • 70 mg/week = 2.48 yrs.
    • 35 mg/week = 4.97 yrs.
Bisphosphonates, ONJ and Toxicity

• What is toxic level?
  
  – Literature states most oral B-ONJ occurs around 2 to 3 years (70 mg/week) or 5 years (35 mg/week)

• Bisphosphonates vary in potency (see next slide!)
BISPHOSPHONATES AND INHIBITION OF BONE RESORPTION

TABLE 1. Relative potency of bisphosphonates with respect to inhibition of bone resorption and FPP synthase activity

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Bone resorption, IC_{50} (μM)</th>
<th>FPP synthase, IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>0.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Alendronate</td>
<td>0.05</td>
<td>0.50</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>0.02</td>
<td>0.31</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>0.002</td>
<td>0.02</td>
</tr>
</tbody>
</table>

FPP, farnesyl diphosphonate.

* Inhibition of 1,25-dihydroxyvitamin D_3-induced calcium release from mouse calvaria in vitro. Data represent mean of 2–6 experiments. Data from Green et al.\textsuperscript{46}

† Mean values calculated from dose–response plots of inhibition of FPP synthase in J774 cell homogenates based on three experiments. Data from Dunford et al.\textsuperscript{45}

Am J Clin Oncol (CCT), Vol 25, No. 6 Suppl 1, 2002
Bisphosphononates, ONJ and Toxicity

• Based on this information:

  • After 5 years (35 mg/week) \(\rightarrow\) 3.36 nmol/ml

  • After 3 years (70 mg/week) \(\rightarrow\) 4.032 nmol/ml

• Or, 3.36 \textit{times} and 4.032 \textit{times} the toxicity level of oral epithelium
ONJ Hypothesized Gene

• Matrix metalloproteinase 2 (MMP2)
  – MMP2 associated with bone abnormalities
  – Bisphosphonates associated with atrial fibrillation
  – MMP2 only gene known to be associated with both bone abnormalities and atrial fibrillation
  – Known disorder-gene associations indicates that cardiovascular disease and bone disease are closely related

Components of BONJ

1. Inhibition of angiogenesis/vasculargenesis

2. Inhibition of osteogenesis/resorption

3. Changes in oral flora competition/Actinomyces

4. Inhibition of normal oral epithelial growth and migration/ supression of endothelial cells/fibroblasts

5. Inhibition of typical immune function/inactivation of T-cells

6. Disruptived event in the oral mucosa/oral procedcures surgery
examined may be also attributable. Whatever the actions are, the results of our study suggest that bisphosphonates modulate oral bacterial behaviors. Zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation and adhesion to hydroxyapatite of oral bacteria, without causing osteonecrosis of the jaw, in mice

Yasuyoshi Kobayashi · Toru Hiraga · Akimi Ueda · Liyang Wang · Michiyo Matsumoto-Nakano · Kenji Hata · Hirofumi Yatani · Toshiyuki Yoneda
Changes in Oral Flora Competition/Actinomyces
Journal of Oral and Maxillofacial Surgery 66(4)
**Conclusion:** In patients taking oral bisphosphonates, a failure to integrate or subsequent loss of integration may occur when oral bisphosphonates are started after successful implant placement. The rate of failure is low, at less than 1%.
evidence to support this practice. Our patient’s necrotic bone showed significant healing 4 months after the start of teriparatide treatment. It is likely that because of its anabolic effects on the bone, administration of this medication may be useful in the clinical setting of osteoporosis and ONJ. Clinical trials are needed to test this hypothesis.

Corresponding author e-mail: jcorreia@uab.edu

Spec Care Dentist 30(2): 77-82, 2010
BISPHOSPHONATES AND INHIBITION OF BONE RESORPTION

• How to treat?

  – Suggestions:
    • No implants or elective surgery on patients taking Zometa or Aredia
    • Delay implants or elective surgery on pts. with high doses of Fosamax – D/C Fosamax prior to surgery then restart Fosamax at a later time
    • Test bone turnover for global picture of bone cell vitality
Bone Strength

• Combination of Bone Mineral Density (BMD) and bone quality

• BMD = grams of mineral per area or volume

• Bone quality = characteristics of the bone matrix (micro-architecture, bone turnover, micro-damage accumulation, degree of calcification and collagen)
Bone Turnover Markers

• Change earlier than BMD
• More consistent results than BMD
• Bone Resorption markers
  – DPD(urinary), NTX(serum/urinary), CTX(urinary)
• Bone formation markers
  – BAP (Bone alkaline phosphatase)(serum)
  – PINP (type I procollagen-N-propeptide)(serum)
• Bisphosphonates
• Raloxifene,
• Estrogen
CTX Lab Values
(C-terminal cross-linked telopeptide)

- >150 pg/mL = Minimal Risk
- 100 - 150 pg/mL = Moderate Risk
- <100 pg/mL = High Risk

Standard grafting techniques and dental implant placements can be used if guided by the published serum CTX values.

## Bone Marker Guidelines

### Table 2. Reference ranges for markers of bone turnover

<table>
<thead>
<tr>
<th>Marker</th>
<th>Range</th>
<th>Reference population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone resorption markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPD [18]</td>
<td>2.8–7.6 nmol/mmol·Cr</td>
<td>(Age, 30–44 years; female)</td>
</tr>
<tr>
<td>NTX (urine) [18]</td>
<td>9.3–54.3 nmolBCE/mmol·Cr</td>
<td>(Age, 30–44 years; female)</td>
</tr>
<tr>
<td>NTX (serum) [23]</td>
<td>7.5–16.5 nmolBCE/l</td>
<td>(Age, 40–44 years; female)</td>
</tr>
<tr>
<td>CTX (urine)</td>
<td>40.3–301.4 μg/mmol·Cr</td>
<td>(Age, 30–44 years; female)</td>
</tr>
<tr>
<td><strong>Bone formation markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAP [18]</td>
<td>7.9–29.0 U/l</td>
<td>(Age, 30–44 years; female)</td>
</tr>
<tr>
<td>PINP [23]</td>
<td>15.4–59.9 ng/ml</td>
<td>(Age, 40–44 years; female)</td>
</tr>
</tbody>
</table>

Reference ranges for markers of bone turnover are within the range of the mean ± 1.96 SD established for healthy premenopausal women.

Numbers in parentheses indicate the age range of subjects for data collection.

Note: there is interlaboratory variability for each range.

BCE, bone collagen equivalent

*EIA method
Lab Perscription

• Please obtain the following lab tests and fax results to my office (fax: xxx-xxx-xxxx)

1. sNTX (serum cross-linked N-telopeptides of type I collagen)

2. sBSAP (serum bone specific alkaline phosphatase) - NOTE: this is not a total alk phos with a bone fraction
PRP and ONJ

• PRP has been shown to be successful in treating ONJ

• Success due to growth factors that stimulate soft tissue healing, promote angiogenesis
ONJ - Other Drugs

- Monoclonal antibodies
  - Denosumab
    - Incidence of ONJ following similar to bisphosphonate therapy
  - Bevacizumab

- Multikinase inhibitor
  - Sunitinib
Denosumab (Prolia™) (den OH sue mab)

• Newer bone antiresorptive agent
• Monoclonal antibody
• FDA approved for:
  – Osteoporosis
  – Metastatic cancer of bone
• Given as a subcutaneous injection twice a year
• Inhibits the RANK ligand - a key regulator of bone-resorbing osteoclasts
Denosumab - Why should we care?

- Approved by the FDA
- Multiple cases relate its use with osteonecrosis of the jaws
- All Dentists (General and Specialists) must understand:
  - denosumab’s mechanism of action & pharmacokinetics
  - Similarities and differences with bisphosphonates
Figure: PTH stimulates the osteoblast to secrete RANKL, which then goes on to stimulate the osteoclast precursor to become active. OPG is a competitive inhibitor of RANKL, and thus blocks it from activating the osteoclast. PTH is secreted by some forms of cancer, included breast carcinoma.
MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

The relationship of denosumab pharmacology and osteonecrosis of the jaws

John Malan, DDS, Kyle Ettinger, DDS, Erich Naumann, DMD, and O. Ross Beirne, DMD, PhD, Okinawa, Japan; Rochester, Minnesota; Kirkland, Washington; and Seattle, Washington

U.S. Navy, Mayo Clinic, and University of Washington
Case Report

• 67-year-old male

• Exposed bone in the maxilla and mandible 6-months following the removal of teeth #’s 3, 4, 5, & 30

• Hypertension, obesity, prostate cancer

• No bisphosphonates or radiation

• 40-pack/year history of tobacco use

• Meds: HCTZ, lisinopril, metoprolol, ibuprofen, calcium, vitamin D supplements
Case Report

• Chlorhexidine gluconate for exposed bone in jaw

• Goserelin acetate - 3 years - (Gonadotropin releasing hormone agonist) treatment of prostate cancer

• Denosumab (Xgeva) for 22 months prior to ONJ - stopped denosumab 4 months post-tooth extractions (26 total injections)
Case Report

- Presented for treatment of ONJ 6 months following tooth removal
- No facial edema
Bevacizumab, Sunitinib, & Denosumab

- All 3 of these drugs have been reported to cause ONJ when administered in isolation or found to increase the severity of ONJ when given in conjunction with bisphosphonates.

- 55 bevacizumab cases of ONJ among 800,000 patients

- 30 Sunitinib-related ONJ in 100,000 patients
Denosumab (Prolia®)

- Monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL)
Denosumab (Prolia®)

- Prevention of skeletal-related events in bone metastases from solid tumors
- Treatment of osteoporosis in postmenopausal females (Prolia™):
- Prevention of androgen-induced bone loss in nonmetastastic prostate cancer
- Prevention of aromatase inhibitor-induced bone loss in nonmetastastic breast cancer (unlabeled use)
Labeling on denosumab

• ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia. An oral exam should be performed by the prescriber prior to initiation of Prolia. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia.

• For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive a thorough examination should receive care by a dentist or an oral surgeon.
Conclusion: Both agents at optimal concentrations did not enhance protective effects of the individual treatments. At sub-optimal (10^{-9} M) concentrations, neither agent alone provided significant protection, but in combination...
Pancreatic hormones
Diabetes Type I and II
In Dentistry
DIABETES MELLITUS

• > 18.4% Population over age 65 have some form of diabetes

• Diabetes type 2 IS ↑ 6% per year
  • Ref. Rees 2000

• Complications

  • Retinopathy, nephropathy, neuropathy, micro- and macro-vascular disease, altered wound healing
Obesity

Vasculature

Adipocytes

Adipokines

FFAs

Inflammation

Insulin resistance

Pancreatic islet

β-cells

Insulin secretion by β-cells

Normal

Increased

Decreased

Blood glucose

Normal

Normal to impaired glucose tolerance

Diabetes mellitus

Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
Natural Course of Diabetes

Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
Diagnosing Diabetes

- Fasting (8 hours) blood glucose $>126$ mg/dl
- Random blood glucose $> 200$ mg/dl
- 4 hour Post prandial glucose $>140$ mg/dl
SUCCESS RATES AND DIABETES MELLITUS

- IMPLANT SUCCESS RATES 85.6% (Fiorellini et al., 2000) to 94.3% (Balshi & Wollfinger, 1999)

- EARLY IMPLANT FAILURE RATE 3.2% vs. LATE IMPLANT FAILURE RATE 5.4% (Esposito et al., 1997)

- VARIOUS REPORTS SHOW INCREASED FAILURE RATE AFTER 1 YEAR (Fiorellini et al., 2000; Morris et al., 2000; Shernoff et al., 1994)
SUCCESS RATES AND DIABETES MELLITUS

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DIABETES MELLITUS

ANIMAL STUDIES

- SIGNIFICANTLY REDUCED BONE-TO-IMPLANT CONTACT IN UNCONTROLLED DIABETICS vs. NON-DIABETICS
  - Nivens et al., 1998; Takeshita et al., 1998

- INSULIN-CONTROLLED DM HAD GREATER BONE DENSITY THAN IN NON-DM CONTROLS
  - Fiorellini et al., 1999

- FOR DM OSSEOINTEGRATION WAS REDUCED 10° IN TRABECULAR BONE, WHEREAS NO DIFFERENCES WERE SEEN IN CORTICAL BONE
  - McCracken et al., 2000
differences in the production of cytokines. In 138 diabetic patients, 255 implants were presented with second degree mobility 90 days after surgery while the same was demonstrated in 48 out of 346 implants from the healthy subjects. These implants were considered failures and were extracted. Implant failure in diabetics was significantly greater than that in non-diabetics when multiple adjoining implants were placed.

**Full Length Research Paper**

**The impact of diabetes on the success of dental implants and periodontal healing**

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CONCLUSION: The evidence reviewed supports diabetes having an adverse effect on periodontal health and periodontal infection having an adverse effect on glycemic control and incidence of diabetes complications. Further rigorous study is necessary to establish unequivocally that treating periodontal infections can contribute to glycemic control management and to the reduction of the burden of diabetes complications.

*Oral Diseases (2008) 14, 191–203*
Results: Evidence on the association between diabetes and periodontitis supports the concept of increased severity but not extent of periodontitis in subjects with poorly controlled diabetes. Subjects with controlled diabetes do not show an increase in extent and severity of periodontitis. Periodontitis is associated with poor glycaemic control and diabetes-related complications. It is inconclusive that periodontal therapy with or

Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks

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Results: In all experimental groups, at the GBR treated sites, significant neo-osteogenesis was observed. The vertical height of the newly formed bone and per cent bone-to-implant contact were not statistically significantly different among the H (51.3 ± 7.2% and 50 ± 6.8%), D (30.5 ± 13.4% and 35 ± 16.8%) and CD (41.6 ± 8.3% and 39.9 ± 6.5%) groups. However, uncontrolled diabetes was related to higher outcome variability and increased rate of infectious complications. In the control sites, marginal bone loss was observed in the D group, whereas, in the H and CD groups, minimal new bone formation was observed.

guided bone regeneration
DIABETES MELLITUS

- INSULIN DEFICIENCY
- HYPERGlyCEMIA
  - KETOACIDOSIS & ATHEROSCLEROSIS (DUE TO ABSENCE OF INFLUENCE ON LIPID METABOLISM)
- ABSOLUTE
  - TYPE 1 DIABETES
- RELATIVE
  - TYPE 2 DIABETES
    - BETA CELLS SYNTHESIZE INSULIN BUT AN INADEQUATE AMOUNT
    - OR TISSUES ARE RESISTANT TO INSULIN ACTION
INSULIN

- PURPOSE – TRANSPORT GLUCOSE INTO CELLS WHERE IT CAN BE USED FOR ENERGY REACTIONS

- IN SKELETAL MUSCLE & LIVER GLUCOSE IS STORED AS GLYCOGEN FOR LATER USE
  - THIS CAN RESULT IN HYPOGLYCEMIA
TYPE 1 DIABETES

- IDDM
- Rx: INSULIN
  - RAPID ACTING
    - LISPRO
  - SHORT ACTING
    - REGULAR, SEMILENTE
  - INTERMEDIATE ACTING
    - NPH, LENTE
  - LONG ACTING
    - PZI, ULTALENTE
SURGERY REQUIREMENTS

- REVIEW HbA$_{1C}$ (IDEAL <7 mg%)

- STABLE DM, KNOWLEDGABLE PATIENT, NOT EXTENSIVE PROCEDURE & WITHIN YOUR COMFORT LEVEL – ? NEED FOR CONSULT

- IF NOT STABLE, POOR KNOWLEDGE BASE FOR PATIENT, EXTENSIVE PROCEDURE – CONSULT
Insulin Diabetic Patient Surgery Requirements

- Eat a light breakfast - do surgery in a.m.
- Half (2/3) the dose of A.M. intermediate insulin
- Check blood glucose level in office prior to beginning surgery
- Plasma glucose level 100-140 preferred
- Use D5W
- Plasma levels may remain elevated for 3-4 days, especially if steroids are used, but attempt to keep between 80 and 140

Type II Diabetes Drugs

- Sulfonylureas
- Biguanides
- Thiazolidinediones
- α-glucosidase inhibitors
- Meglitinides
- DPP-4 inhibitors
SURGERY REQUIREMENTS

- REVIEW HbA$_{1C}$ (IDEAL <7 mg%)

- STABLE DM, KNOWLEDGABLE PATIENT, NOT EXTENSIVE PROCEDURE & WITHIN YOUR COMFORT LEVEL – ? NEED FOR CONSULT

- IF NOT STABLE, POOR KNOWLEDGE BASE FOR PATIENT, EXTENSIVE PROCEDURE – CONSULT
Diabetes Controlled with Oral Agents

- Hold medication day of surgery
- Eat a light breakfast - do surgery in a.m.

Top 25 Drugs 2013

James L. Rutkowski DMD, PhD
Top 25 Drugs by Spending

Total US Market $307.4 B
#1 Lipitor (Atorvastatin) $7.2B

- Antilipemic agent (HMG-CoA Reductase inhibitor)
- Inhibits the rate limiting enzyme in cholesterol synthesis (reduces production of mevalonic acid from HMG-Co-A)
- Results in a compensatory ↑ in LDL receptors on hepatocyte membranes and stimulation of LDL catabolism.
- Drug interaction with macrolides
#2 Nexium (Esomeprazole) $6.3B

- Proton pump inhibitor - suppresses gastric acid secretion by inhibition of the $\text{H}^+/\text{K}^+$ ion exchange pump

- Xerostomia - normal salivary flow resumes upon discontinuation

- High dose long-term interferes with bone repair
#3 PLAVIX® - CLOPIDOGREL $6.1 B

• BLOCKS THE ADP RECEPTOR WHICH PREVENTS THE BINDING OF FIBRINOGEN TO THAT SITE

• DOES NOT ALTER THE RECEPTOR

• REDUCES # OF FUNCTIONAL ADP RECEPTORS
PLAVIX® - CLOPIDOGREL

• MONITOR WITH PLATELET AGGREGATION - ? value
• INITIAL 2 TO 4 WEEKS MAY CAUSE THROMBOCYTOPENIA
  – CHECK PLATELETS
• RARELY NECESSARY TO D/C
• SURGERY IF MULTIPLE SITES OR EXTENSIVE ? – get consultation
  – DISCONTINUE 7 DAYS PRIOR TO PROCEDURE (RARELY NECESSARY!)

James L. Rutkowski D.M.D., Ph.D.
PLAVIX® - CLOPIDOGREL - WOW!!!!

- 30% of population has a genetic variant in liver metabolizing enzymes that affect efficacy of clopidogrel - no effect at all
  - CYP2C19 converts clopidogrel to an active metabolite.
  - Genes which encode and express liver enzymes responsible for metabolism exist in several polymorphic states (CYP2C19 has 4 variants with reduced function)
  - Relative reduction of 32% in active metabolite
  - 53% higher risk for primary efficacy outcome of death from cardiovascular causes, MI, stroke
  - Stent thrombosis in carriers 3 X that of non-carriers
Prasugrel (Effient™)

• Antiplatelet agent and aggregation inhibitor
  —For ↓ thrombotic cardiovascular events (stent thrombosis)

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel Non-fatal subsequent heart attacks</th>
<th>Prasugrel Non-fatal subsequent heart attacks</th>
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<tbody>
<tr>
<td></td>
<td>9.1%</td>
<td>7%</td>
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<tr>
<td>Deaths and strokes</td>
<td>equal</td>
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<tr>
<td>Risk of significant</td>
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<tr>
<td>fatal bleeding</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>
Prasugrel (Effient™)

• Pro-drug
• Irreversibly blocks P2Y12 component of adenosine diphosphate (ADP) receptors on platelets for their lifespan
  – ↓ platelet activation and platelet aggregation
  – Normal platelet activity does not return (new platelets in 5 to 9 days after D/C
  – Loading dose 60 mg followed by maintenance dose of 10 mg daily.
  – Should take with ASA 75 to 325 mg daily
Prasugrel (Effient™)

• Genetic variants in liver metabolizing enzymes do not affect efficacy
  – Undergoes rapid intestinal and serum metabolism via esterase-mediated hydrolysis to a thiolactone (inactive metabolite), which is then converted, via CYP3A4 & CYP2B6 enzyme oxidation, to the active metabolite designated as R-138727.
Ticagrelor (Brilinta®)

- Reduce rate of thrombotic cardiovascular events in pts with acute coronary syndrome (ACS): unstable angina, non-ST elevation MI, ST elevation MI
- More effective than clopidogrel
Ticagrelor (Brilinta®)

• Drug interactions
  – Inhibitors of CYP3A4
  – Ketocanazole
  – Itaconazole
  – Voriconazole
  – Clarithromycin (Biaxin®)
  – Erythromycin

• NSAIDs
Ticagrelor (Brilinta®)

- Mechanism: An active, reversible platelet inhibitor
- CYP3A4 converts ticagrelor to another active reversible platelet inhibitor - which is the major active metabolite
- Act at the ADP-receptor
- Loading dose 180 mg then 90 mg BID
  - Give with loading dose ASA 325 mg then 75 - 100 mg. Daily
  - ASA doses above 100 mg/day reduce effectiveness of ticagrelor and should be avoided
Ticagrelor (Brilinta®)

- Dental considerations
- Do NOT D/C without consultation
- Expect bleeding and echymosis
- Pts often have SOB
- No coagulation parameters suggested
dabigatran (Pradaxa®)

Boehringer Ingelheim

- For prevention of stroke and systemic embolism (blood clots) in patients with atrial fibrillation

- first replacement for warfarin (Coumadin®) since Coumadin was approved in 1954.
Serine protease
dabigatran (Pradaxa®) anticoagulant

- acts by inhibiting thrombin, an enzyme in the blood that is involved in blood clotting
- thrombin (serine protease) enables the conversion of fibrinogen to fibrin during the coagulation cascade, its prevention prevents the development of a thrombus.
- recommended dose is a 150 mg capsule taken orally
- Warfarin therapy requires patients to undergo periodic monitoring with blood tests
  - INR monitoring not necessary for dabigatran.
dabigatran (Pradaxa®)

- Measure of Effect
  - At therapeutic doses prolongs the activated partial thromboplastin time (aPTT)
  - Oral dose of 150 mg twice daily, the median peak aPTT is approximately twice that of control values
  - Twelve hours after the last dose, the median aPTT is 1.5x control
  - INR test is relatively insensitive to the activity of dabigatran and may not be elevated in patients on dabigatran.
dabigatran (Pradaxa®)

Absorption and Metabolism

- After swallowing a dabigatran (Pradaxa) capsule, peak blood level occurs in 1 hour. The half-life is 12 to 17 hours.

- Not metabolized by CYP enzymes

- After oral administration, dabigatran etexilate is converted to dabigatran through esterase-catalyzed hydrolysis of the molecule in plasma

- Dabigatran is not a substrate, nor inhibitor, nor inducer of CYP 450 enzymes
Dabigatran and Risk of Bleeding

- ↑ risk of bleeding and can cause significant, and sometimes fatal, bleeding
- Drugs that can increase the risk of bleeding include antiplatelet agents and chronic use of NSAIDs
- RE-LY trial, life-threatening bleeding occurred at an annualized rate of 1.5% for Pradaxa 150 mg and 1.8% for warfarin.
- Discontinuing Pradaxa for surgery places the patient at an ↑ risk of stroke
  - If anticoagulation must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.
- Dental patients who may have a high risk of bleeding if taking Pradaxa include those over 75 years of age, or are taking aspirin, or long term NSAIDs, or clopidogrel (Plavix®) or prasugrel (Effient®).
#4 Advair Diskus (Salmeterol and Fluticasone)  
$4.7B

• Long acting β2 agonist (bronchodilation)
• Corticosteroid inhalant (anti-inflammatory, immunosuppressive, anti-proliferative, potent vasoconstrictor)
• Act locally - little effect on heart rate
• Dental: Localized infections with *Candida albicans* or *Aspergillus niger* frequently occur in mouth and pharynx
Treating *Candida albicans* or *Aspergillus niger* infections

- Diflucan (fluconazole)
  - Loading dose: 200 mg on day 1; maintenance dose 100 mg daily for ≥2 weeks. Note: Therapy with 100 mg daily is associated with resistance development (Rex, 1995).
  - Alternative dosing: 100-200 mg daily for 7-14 days for uncomplicated, moderate-to-severe disease; chronic therapy of 100 mg 3 times weekly is recommended in immunocompromised patients with history of oropharyngeal candidiasis (OPC) (Pappas, 2009)

- Dental Use
  - Treatment of susceptible fungal infections in the oral cavity including candidiasis, oral thrush, and chronic mucocutaneous candidiasis treatment of esophageal and oropharyngeal candidiasis caused by Candida species; treatment of severe, chronic mucocutaneous candidiasis caused by Candida species

- Numerous drug interactions
#5 Abilify (Aripiprazole) $4.6B

- Antipsychotic agent
- Exhibits high affinity for D₂, D₃, 5-HT₁A, and 5-HT₂A receptors; moderate affinity for D₄, 5-HT₂C, 5HT₇, alpha adrenergic, and H₁ receptors plus serotonin reuptake transporter
- Partial agonist at the D₂ and 5-HT₁A receptors
- Antagonist at the 5-HT₂A receptor
#5 Abilify (Aripiprazole)

• Effect on dental treatment
  – Extrapyramidal symptoms
  – Xerostomia and changes in salvation (normal salivary flow resumes upon discontinuation)
  – Recomendation: extra fluoride
#6 Seroquel (Quetiapine) $4.4B

- Antipsychotic agent
- Antagonist at the $D_2$ and $5-HT_2$ receptors
- No affinity for the benzodiazepine receptors
- Local anesthesia/vasoconstrictor precautions
  - Prolongs QT interval $\rightarrow$ torsade de pointes
  - Epinephrine effect is unknown, therefore exercise caution!!!!
    - Use epi 1:200,000 - one carpule - observe for 5 minutes
    - Xerostomia (normal flow resumes upon discontinuation
#7 Singulair (montelukast) $4.1B

- Leukotriene-receptor antagonist
- Dental treatment: may cause tooth pain
- Effects on Bleeding: Increased bleeding and thrombocytopenia
- Dose: Adult 10 mg once a day
#7 Singulair (montelukast)

- Mechanism of Action: Selective leukotriene receptor antagonist that inhibits the cysteiny1 leukotriene receptor. Cysteiny1 leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Cysteiny1 leukotrienes are also released from the nasal mucosa following allergen exposure leading to symptoms associated with allergic rhinitis.
#8 Crestor (Rosuvastatin) $3.8B

- Antilipemic agent
- Inhibits the rate limiting enzyme in cholesterol synthesis (reduces production of mevalonic acid from HMG-Co-A)
- Results in a compensatory ↑ in LDL receptors on hepatocyte membranes and stimulation of LDL catabolism.
#9 Actos (piogliazone) $3.5B

- Thiazolidinedione antidiabetic agents
- Improves target cell response to insulin without increasing pancreatic insulin secretion
- Effect on dental treatment
  - Tooth pain
  - Appointments in AM to minimize stress-induced hypoglycemia
  - Major procedures - hold drug day of surgery
#10 Epogen (epoetin alfa) $3.3B

- Pharmacologic Category: Colony Stimulating Factor; Erythropoiesis-Stimulating Agent (ESA); Growth Factor; Recombinant Human Erythropoietin

- Use: **Treatment of anemia due to concurrent myelosuppressive chemotherapy in patients with cancer** (nonmyeloid malignancies) receiving chemotherapy (palliative intent) for a planned minimum of 2 additional months of chemotherapy; **treatment of anemia due to chronic kidney disease** (including patients on dialysis and not on dialysis) to decrease the need for RBC transfusion; **treatment of anemia associated with HIV** (zidovudine) therapy when endogenous erythropoietin levels ≤500 mUnits/mL; reduction of allogeneic RBC transfusion for elective, noncardiac, nonvascular surgery when perioperative hemoglobin is >10 to ≤13 g/dL and there is a high risk for blood loss
#10 Epogen (epoetin alfa)

• **Mechanism of Action**
  - Induces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells
  - Induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature to erythrocytes.
#11 Remicade (Infliximab) $3.3B

- Pharmacologic Category
  - Antirheumatic, Disease Modifying; Gastrointestinal Agent, Miscellaneous; Immunosuppressant Agent; Monoclonal Antibody; Tumor Necrosis Factor (TNF) Blocking Agent

- Effects on Bleeding
  - associated with thrombocytopenia, anemia, and hemolytic anemia
#11 Remicade (Infliximab)

– Mechanism of Action

• Chimeric monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα), thereby interfering with endogenous TNFα activity

• Elevated TNFα levels have been found in involved tissues/fluids of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn’s disease and ulcerative colitis

• Biological activities of TNFα include the induction of proinflammatory cytokines (interleukins), enhancement of leukocyte migration, activation of neutrophils and eosinophils, and the induction of acute phase reactants and tissue degrading enzymes
#11 Remicade (Infliximab)

- Infections: [U.S. Boxed Warning]
  - increased risk for serious infections

- infections usually developed in patients receiving concomitant immunosuppressive agents (eg, methotrexate or corticosteroids) and may present as disseminated (rather than local) disease

- Monitor closely for signs/symptoms of infection. Discontinue for serious infection or sepsis

- Consider 7- to 10-day antibiotic coverage for dental surgeries
#12 Enbrel (etanercept) $3.3B

- Pharmacologic Category
  - Antirheumatic, Disease Modifying; Tumor Necrosis Factor (TNF) Blocking Agent

- Use
  - Treatment of moderately- to severely-active rheumatoid arthritis (RA); moderately- to severely-active polyarticular juvenile idiopathic arthritis (JIA); psoriatic arthritis; active ankylosing spondylitis (AS); moderate-to-severe chronic plaque psoriasis
#12 Enbrel (etanercept)

– Mechanism of Action
  
  • a recombinant DNA-derived protein composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1
  
  • binds tumor necrosis factor (TNF) and blocks its interaction with cell surface receptors.
#12 Enbrel (etanercept)

• infections: [U.S. Boxed Warning]
  – increased risk for serious infections

  – infections usually developed in patients receiving concomitant immunosuppressive agents (eg, methotrexate or corticosteroids) and may present as disseminated (rather than local) disease

  – Monitor closely for signs/symptoms of infection. Discontinue for serious infection or sepsis

  – Consider 7- to 10-day antibiotic coverage for dental
#13 Cymbalta (duloxetine) $3.2B

• Antidepressant

• Potent inhibitor of neuronal serotonin and NE reuptake and weak inhibitor of dopamine reuptake

• Local Anesthetic/vasoconstrictor precautions
  – With inhibition of NE reuptake - use caution with epi
    • Use 1:200,000 one carpule and monitor

• Xerostomia and changes in salivation (normal flow returns upon discontinuation
#13 Cymbalta (duloxetine)

- May impair platelet aggregation → risk of bleeding especially if used with NSAIDs
- Bleeding has been reported to range from minor bruising and epistaxis to life-threatening hemorrhage
- No need to discontinue for dental treatment - be aware of a potential for a prolonged bleeding time
- NSAIDs drug interaction is a Risk level C : Monitor therapy
#14 Avastin (bevuhsizuhmab) #3.1B

- **Pharmacologic Category**
  - Antineoplastic Agent, Monoclonal Antibody; Vascular Endothelial Growth Factor (VEGF) Inhibitor

- **Use**
  - Treatment of metastatic colorectal cancer (first-or second-line treatment and second-line after progression on a first-line treatment containing bevacizumab); treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous, nonsmall cell lung cancer; treatment of progressive glioblastoma; treatment of metastatic renal cell cancer (not an approved use in Canada)
#14 Avastin (bevuhhsizuhmab)

– Mechanism of Action

• a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR

• VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels)

• inhibition of microvascular growth is believed to retard the growth of all tissues
#14 Avastin (bevuhsizuhmab)

— Effects on Dental Treatment

• Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, taste disorder
• Minor gum bleeding has been reported in 2% to 4% of patients
• Thrombocytopenia has been reported
• osteonecrosis of the jaw (ONJ)
#14 Avastin (bevuhsizuhmab)

- Three case reports describe the development of ONJ in association with bevacizumab therapy
- All cases were cancer patients treated with bevacizumab 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks (Estilo, 2009; Greuter, 2008)
- Another report showed that a combination of bisphosphonates and antiangiogenic factors (primarily bevacizumab) induces ONJ more frequently than bisphosphonates alone. Of the 25 patients receiving concurrent treatment with bisphosphonates and the antiangiogenic drug bevacizumab, four developed ONJ (16%). Of the 91 patients receiving bisphosphonates without antiangiogenic factors, one developed ONJ (1.1%), a significant statistical difference (Christodoulou, 2009).
#14 Avastin (bevuhsizuhmab)

• Hemorrhage: [U.S. Boxed Warning]
  – Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding have been reported (up to 5 times more frequently if receiving bevacizumab)

• Wound dehiscence: [U.S. Boxed Warning]
  – Incidence of wound healing and surgical complications is increased in patients who have received bevacizumab; discontinue with wound dehiscence. Although the appropriate interval between withholding bevacizumab and elective surgery has not been defined, bevacizumab should be discontinued at least 28 days prior to surgery and should not be reinitiated for at least 28 days after surgery and until wound is fully healed
#15 OxyContin (dihydrohydroxycodeinone; oxycodone) $3.1B

- Binds to CNS opiate receptors $\rightarrow$ inhibition of ascending pain pathways $\rightarrow$ altering pain perception and response
- Produces CNS ↓
- Xerostomia (normal salivary flow resumes upon discontinuation)
- Sedation in dentistry?
#16 Neulasta (pegfilgrastim) $3.0B

- Pharmacologic Category
  - Colony Stimulating Factor

- Use
  - To decrease the incidence of infection, by stimulation of granulocyte production, in patients with nonmyeloid malignancies receiving myelosuppressive therapy associated with a significant risk of febrile neutropenia
#16 Neulasta (pegfilgrastim)

—Mechanism of Action

• Stimulates the production, maturation, and activation of neutrophils
• Activates neutrophils to increase both their migration and cytotoxicity
#17 Zyprexa (olazapoin) $3.0B

- Antimanic and antipsychotic agent
- Potent antagonist at serotonin and dopamine, histamine and α adrenergic receptors
- Weak agonist at benzodiazepine receptors
#18 Humira (adalimyoomab) $2.9B

- **Pharmacologic Category**
  - Antirheumatic, Disease Modifying; Gastrointestinal Agent, Miscellaneous; Monoclonal Antibody; Tumor Necrosis Factor (TNF) Blocking Agent

- **Use**
  - active rheumatoid arthritis (moderate-to-severe)
  - active psoriatic arthritis
  - ankylosing spondylitis
  - Crohn’s disease
  - ulcerative colitis in patients unresponsive to immunosuppressants
  - plaque psoriasis
  - juvenile idiopathic arthritis
#18 Humira (adalimumab)

• Mechanism of Action
  – recombinant monoclonal antibody that binds to human tumor necrosis factor alpha (TNF-alpha), thereby interfering with binding to TNFα receptor sites and subsequent cytokine-driven inflammatory processes
  – Reduces signs and symptoms and maintains clinical remission in Crohn’s disease and ulcerative colitis
  – reduces epidermal thickness and inflammatory cell infiltration in plaque psoriasis.
#18 Humira (adalimumab)

- infections: [U.S. Boxed Warning]
- increased risk for serious infections

- infections usually developed in patients receiving concomitant immunosuppressive agents (eg, methotrexate or corticosteroids) and may present as disseminated (rather than local) disease

- Monitor closely for signs/symptoms of infection. Discontinue for serious infection or sepsis

- Consider 7- to 10-day antibiotic coverage for dental
#19 Lexapro (escitalopram) $2.8B

- Antidepressant
- Inhibits reuptake of serotonin with little to no effect on NE or dopamine
- Xerostomia (normal flow returns upon discontinuation)
#19 Lexapro (escitalopram)

• May impair platelet aggregation → risk of bleeding especially if used with NSAIDs
• Bleeding has been reported to range from minor bruising and epistaxis to life-threatening hemorrhage
• No need to discontinue for dental treatment - be aware of a potential for a prolonged bleeding time
• NSAIDs drug interaction is a Risk level C : Monitor
#19 Lexapro (escitalopram)

- Opioid analgesics - may enhance the serotonergic effect → serotonin syndrome *Risk level C*: Monitor therapy
- Macrolide antibiotics may decrease metabolism of escitalopram; *Risk level C*: Monitor therapy
  - Exception azithromycin
#20 Rituxan (rituximab) $2.8B

- Pharmacologic Category
  - Antineoplastic Agent, Monoclonal Antibody; Antirheumatic Miscellaneous; Immunosuppressant Agent; Monoclonal Antibody

- Use
  - non-Hodgkin lymphomas (NHL):
  - Relapsed or refractory, low-grade or follicular B-cell NHL (as a single agent)
  - Follicular B-cell NHL Nonprogressing, low-grade B-cell NHL (as a single agent after first-line CVP treatment)
  - Diffuse large B-cell NHL Treatment of CD20-positive chronic lymphocytic leukemia (CLL) (in combination with fludarabine and cyclophosphamide)
  - Rheumatoid arthritis (in combination with methotrexate) in adult patients with inadequate response to one or more TNF antagonists
  - Granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis) (in combination with glucocorticoids)
  - Microscopic polyangiitis (MPA) (in combination with glucocorticoids)
#20 Rituxan (rituksimab)

**Effects on Bleeding**
- significant myelosuppression, potentially including significant reduction in platelet counts (thrombocytopenia grades 3/4: 2% to 11%)
- altered hemostasis
- medical consult is suggested

**Mechanism of Action**
- monoclonal antibody directed against the CD20 antigen on B-lymphocytes.
#21 Aricept (donepezil) $2.5B

• Tx Alzheimer’s disease
• Acetylcholinesterase inhibitor
• Reversibly and non-competitively inhibits centrally-active acetylcholinesterase → increased concentrations of acetylcholine available for synaptic transmission in the CNS
• ↑ saliva
#22 Lovenox (eenoksaparin) $2.3B

• Pharmacologic Category
  – Low Molecular Weight Heparin

• Use
  – Acute coronary syndromes: Unstable angina (UA), non-ST-elevation (NSTEMI), and ST-elevation myocardial infarction (STEMI)
  – DVT prophylaxis: Following hip or knee replacement surgery, abdominal surgery, or in medical patients with severely-restricted mobility
  – DVT treatment (acute): Inpatient treatment (patients with and without pulmonary embolism) and outpatient treatment (patients without pulmonary embolism)
#22 Lovenox (eenoksaparin)

- Effects on Bleeding
  - Hemorrhage may occur at virtually any site
  - Routine coagulation tests, such as prothrombin time (PT) and aPTT, are relatively insensitive measures of enoxaparin injection activity and, therefore, unsuitable for monitoring
  - Moderate thrombocytopenia occurred at a rate of ~1%
  - Medical consult is suggested.
#22 Lovenox (eenoksaparin)

- Mechanism of Action
  - an anticoagulant by enhancing the inhibition rate of clotting proteases by antithrombin III impairing normal hemostasis and inhibition of factor Xa
  - Low molecular weight heparins have a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa

- No NSAIDS
#23 Atripla (efavirenz) $2.2B

• Pharmacologic Category
  – Antiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside); Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside); Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleotide)

• Use
  – HIV infection
#23 Atripla (efaverenz)

- Effects on Dental Treatment
- xerostomia (normal salivary flow resumes upon discontinuation)
- abnormal taste
#24 Copaxone (glatirameracetate) $2.2B

- **Pharmacologic Category**
  - Biological, Miscellaneous

- **Use**
  - Management of relapsing-remitting type multiple sclerosis, including patients with a first clinical episode with MRI features consistent with multiple sclerosis
#24 Copaxone (glatirameracetate)

- Effects on Dental Treatment
  - Ulcerative stomatitis, salivary gland enlargement, and oral moniliasis

- Mechanism of Action
  - induces and activate T-lymphocyte suppressor cells specific for a myelin antigen
  - interferes with the antigen-presenting function of certain immune cells opposing pathogenic T-cell function
#25 Spiriva $2.0B

- Competitively and reversibly inhibits the action of acetylcholine at muscarinic receptors (M₃) in bronchial smooth muscle → bronchodilation

- Xerostomia (normal saliva flow resumes upon discontinuation)
Other Drugs to Know
Lantus (Insulin glargine)

• Long-acting insulin analog
• Patients with type I diabetes should be appointed in the morning to minimize chance of stress-induced hypoglycemia
  – Make certain they eat something unless deep/general anesthesia
Lyrics (pregabalin)

• Analgesic, anticonvulsant

• Binds to $\alpha_2\Delta$ subunits of voltage-gated calcium channels in CNS, inhibiting excitatory neurotransmitter release

• Structurally related to GABA - does not bind to GABA or benzodiazepine receptors
Lyrics (pregabalin)

- Antinociceptive and anticonvulsant activity
- ↓ symptoms of peripheral neuropathies
- ↓ frequency of seizures
- Xerostomia and changes in salivation (normal flow returns upon discontinuation)
- Bleeding - may rarely be associated with thrombocytopenia
Diovan (valsartan)

- Tx hypertension
- Angiotensin II receptor blocker
- Antagonist at angiotensin II (AT2) receptors
  - Displaces angiotensin II from the AT1 receptor and produces ↓BP by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses.
  - Results in more efficient blockade of the cardiovascular effects of angiotensin II and fewer side effects than the ACE inhibitors.
Diovan (valsartan)

- NSAID - valsartan drug interaction
  - NSAIDs may diminish receptor blockade, glomerular filtration and renal function
  - *Risk level C*: Monitor therapy
NSAIDs - Antihypertensive Drug Interaction

• An analysis of >12 randomized trials of antihypertensive therapy found that a 20% to 40% reduction in cardiovascular disease required only a 5- to 6-mm-Hg decrease in diastolic BP.

• This magnitude of BP reduction is typically seen with any single antihypertensive drug treatment.

• It is also represents the usual increase in BP seen when nonsteroidal anti-inflammatory drugs (NSAIDs) interact with antihypertensive drugs.

• Horne, Hansten; Pharmacy Times April 2006
Effexor XR (venlafaxine)

- Antidepressant
- Potent inhibitor of neuronal serotonin and NE reuptake and weak inhibitor of dopamine reuptake
- Active metabolite o-desmethylvenlafaxine (ODV)
Effexor XR (venlafaxine)

- Local anesthetic/vasoconstrictor precaution:
  - Blockade of NE reuptake in CNS synapses may lead to an ↑ BP
  - Venlafaxine has been known to produce a sustained increase in diastolic BP and HR as a side effect
  - ∴ administer epinephrine with caution
    - Use 1:200,000 monitor BP and HR
Effexor XR (venlafaxine)

• May impair platelet aggregation → risk of bleeding especially if used with NSAIDs
• Bleeding has been reported to range from minor bruising and epistaxis to life-threatening hemorrhage
• No need to discontinue for dental treatment - be aware of a potential for a prolonged bleeding time
• NSAIDs drug interaction is a Risk level C : Monitor
Concerta (methilfenidate)

• CNS stimulant
• Up to 10% of patients taking amphetamine-like drugs may present with hypertension.
• ∴ monitor BP prior to using vasoconstrictor (monitor intra-procedure also)
Levaquin (levofloxacin)

• Fluoroquinolone antibiotic
• Inhibits DNA-gyrase in susceptible organisms thereby inhibits relaxation of supercoiled DNA and promotes breakage of DNA strands.
• DNA gyrase (topoisomerase II) is an essential bacterial enzyme that maintains the superhelical structure of DNA and is required for DNA replication and transcription, DNA repair, recombination and transposition
Levaquin (levofloxacin)

• Levofloxacin prolongs QT interval and can cause torsade de pointes

• Is is not known what effect vasoconstrictors in local anesthetic (Epi) will have on patients with a known history of congenital prolonged QT interval or in patients taking medications that prolong QT interval

• :: use epi 1:200,000 and monitor
Celebrex - celecoxib

- COX-2 selective NSAID
- Inhibits prostaglandin synthesis by ↓ the activity of COX-2 resulting in decreased formation of prostaglandin precursors
- Analgesic, anti-inflammatory, and antipyretic properties
- Does not inhibit COX-1 at normal doses, but may at high doses
Celebrex - celecoxib

- Stomatitis, abnormal taste, xerostomia (normal flow resumes upon discontinuation)
- Tooth pain
- May enhance the adverse/toxic effect of other NSAIDs given simultaneously
- Risk level C: Monitor therapy
Celebrex - celecoxib

- Since COX-2 and not COX-1 is inhibited there may not be a bleeding issue
- COX-1 is involved in platelet aggregation
- Doses up to 800 mg and multiple doses of 600 mg twice a day had no effect on platelet aggregation or bleeding time.
- Naproxen 500 mg BID, ibuprofen 800 mg TID, or diclofenac 75 mg BID significantly reduced platelet aggregation and prolonged the bleeding time

James L. Rutkowski, D.M.D., Ph.D.
Diovan HCT
(valsartan/ hydrochlorothiazide)

• Same as #18 Diovan except with hydrochlorothiazide (HCT)
• HCT may cause hypokalemia - resulting in cardia arrhythmia
  – Use vasoconstrictors (epi) with caution
  – Recommendation: use epi 1:200,000 and monitor
Januvia (sitagliptin)

• Antidiabetic agent [dipepidyl peptidase IV (DPP-IV) inhibitor

• Inhibits DPP-IV enzyme resulting in prolonged active incretin levels [incretin regulates glucose homeostasis by ↑ insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells]

• Incretin is normally inactivated by DPP-IV enzyme
Januvia (sitagliptin)

- Sitagliptin-dependent patients should be appointed for dental treatment in morning to minimize chance of stress-induced hypoglycemia
- May want to hold day of surgery
- Make sure patient eats unless deep/general anesthesia
Januvia (sitagliptin)

• Corticosteroids may diminish the hypoglycemic effect which can lead to ↑ blood glucose levels
• OR - if prolonged corticosteroid use and get HPA axis suppression, then may have episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use
  —Risk level C: Monitor therapy
Suboxone (buprenorphine and naloxone)

• Sublingual administration for opioid dependence
• Sedative effects may be potentiated with conscious sedation techniques
REALITY

• “Expected changes in the nation’s demographics, patient populations and drug consumption make a comprehensive review and evaluation of drug interactions in dental practice particularly timely”
  – JADA January 1999

• Keeping up with the volume of new medications, the aging population, and the increased number of medications taken by patients results in a nearly impossible task. Non-the-less, as clinicians we are expected to know enough to protect the patient during treatment appointments.
Drugs used in the Management of Hypertension

Diuretics
Beta-Blockers
Combined Alpha and Beta Blockers
Angiotensin-Converting Enzyme Inhibitors (ACEIs)
Angiotensin Receptor Blockers (ARBs)
Calcium Channel Blockers (CCBs)
Alpha Blockers
Central Alpha$_2$ Agonists and Other Centrally Acting Drugs
Direct Vasodilators

James L. Rutkowski DMD, PhD
NSAIDs - Antihypertensive Drug Interaction

- An analysis of >12 randomized trials of antihypertensive therapy found that a 20% to 40% reduction in cardiovascular disease required only a 5- to 6-mm-Hg decrease in diastolic BP.

- This magnitude of BP reduction is typically seen with any single antihypertensive drug treatment.

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- Horne, Hansten; Pharmacy Times April 2006
NSAIDs + Antihypertensives

- NSAIDs can interfere with renal perfusion and PGI\textsubscript{2} (prostacyclin)
- Interfere with action of antihypertensive agent
- Result is an increase in BP
- Occurs usually in 4 to 9 days
Beta Blockers (BBs)

- Nonselective
  - Propranolol (Inderal®)
  - Timolol (Blocadren®)
  - Nadolol (Corgard®)
  - Pindolol (Visken®)
Non-selective $\beta$ blockers & Epinephrine

- Oral manifestations
  - Taste changes, lichenoid reactions
- Other considerations
  - Avoid prolonged use of NSAIDs - Hypertensive effects

James L. Rutkowski DMD, PhD
Non-selective β blockers - Epinephrine Interaction

• Propranolol provides blockade of $\beta_1$- and $\beta_2$-receptors

• Does not alter $\alpha$-action

• Addition of epinephrine ($\alpha$, $\beta_1$, $\beta_2$-action) leads to unopposed $\alpha$ action

• Resulting in MASSIVE VASOCONSTRICTION = possible HYPERTENSIVE CRISIS
Non-selective β blockers & Epinephrine
Selective $\beta_1$ Blockers (Cardioselective)

- Meoprolol (Lopressor®)
- Acebutolol (Sectral®)
- Atenolol (Tenormin®)
- Betaxolol (Kerlene®)
- Bisoprolol (Zebeta®)

James L. Rutkowski DMD, PhD
Selective $\beta_1$ Blockers (Cardioselective)

- Vasoconstrictor interactions
- Cardioselective - normal use
- Oral Manifestations
  - Taste changes, lichenoid reactions
- Other considerations
  - Avoid prolonged use of NSAIDs
    - May reduce antihypertensive effects

James L. Rutkowski DMD, PhD
## Logical Combinations

<table>
<thead>
<tr>
<th></th>
<th>Diuretic</th>
<th>β-blocker</th>
<th>CCB</th>
<th>ACE inhibitor</th>
<th>α-blocker</th>
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<tr>
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</tbody>
</table>

* Verapamil + beta-blocker = absolute contra-indication
Aspirin for Cardioprotection: Latest Recommendations from the U.S. Preventive Services Task Force

• Known:

• Heart attack and stroke are the leading causes of death in the United States.

• ASA is effective in ↓ the risk of CVD

• Task Force found good evidence that ASA ↑ the incidence of GI bleeding and fair evidence that ASA ↑ the incidence of hemorrhagic stroke

• Benefits vs risk of ASA use for cardioprotection in adult men and women without a history of coronary heart disease or stroke recommendations are:
• **Women** 55 to 79 years of age to use ASA when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in GI hemorrhage

• **Men** 45 to 79 years of age to use ASA when the potential benefit of a reduction in MI outweighs the potential harm of an increase in GI hemorrhage

• Task Force could not recommend the use of ASA in men and women 80+ years because current evidence is insufficient to assess the balance of benefits and risks of ASA

• Annals of Internal Medicine 2009; 150:396-404.
Men 45-59 Years of Age Taking ASA daily for 10 years

- CHD risk of 1% = 3.2 MIs prevented for every 1000 men and 8 GI bleeding cases
- CHD risk of 5% = 16 MIs prevented for every 1000 men and 8 GI bleeding cases
- CHD risk of 10% = 32 MIs prevented for every 1000 men and 8 GI bleeding cases
- CHD risk of 15% = 48 MIs prevented for every 1000 men and 8 GI bleeding cases.
Women 50-59 Years of Age Taking ASA daily for 10 years

- Stroke risk of 1% = 1.7 strokes prevented for every 1000 women and 4 GI bleeding cases
- Stroke risk of 5% = 8.5 strokes prevented for every 1000 women and 4 GI bleeding cases
- Stroke risk of 10% = 17 strokes prevented for every 1000 women and 4 GI bleeding cases
- Stroke risk of 15% = 25.5 strokes prevented for every 1000 women and 4 GI bleeding cases
• The Task Force recommends against the use of ASA in

• women < 55 years of age for stroke prevention

• Men < 45 years of age for MI prevention

• Reasoning is moderate to high certainty that ASA in these groups have no net benefit or that the harms outweigh the benefits.
Aspirin Daily Dose

- Studies show that doses between 75 and 100 mg daily or 100 mg and 325 mg every other day are beneficial for cardioprotection.

- A dosage of approximately 75 mg daily is as effective as higher doses.

- Risk of GI bleeding may increase with dose, the daily dose of 75 mg would seem to be appropriate.

- ASA is commercially available as the 81 mg "baby" strength product and an 81 mg daily dose is consistent with the task force recommendations.

Ketorolac Nasal Spray (Sprix®)

• 3 studies evaluating the efficacy of ketorolac (nasal spray) for pain relief in postsurgical patients

• Study #1 describes its use in dental oral surgery patients

• Studies #2 & 3 describe its use in medical surgery patients
"Intranasal Ketorolac for Pain Secondary to Third Molar Impaction Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial" - Results

- 54% women; 79% of the subjects were white. The mean age was 24 years.

- At each time point up to 8 hours, the mean pain intensity difference scores were greater for nasal ketorolac than placebo.

- Mean pain relief scores over time (where 0 was no relief and 4 was complete relief) - significantly greater in the ketorolac group compared to the placebo group at all time points, from 20 minutes (1.3 ± 0.2 vs 0.4 ± 0.1) through 8 hours (1.1 ± 0.2 vs 0.4 ± 0.1).

- Global assessment of pain was significantly better in the ketorolac vs placebo, group - 60% of the patients who received ketorolac considered pain control as "good" (20%), "very good" (30%) or "excellent" (10%) vs 13% of patients who received placebo reporting "good" (7.5%) or "very good" (5%) pain control.

- Median time to rescue medication use in the ketorolac group was 360 minutes, compared to 96 minutes in the placebo group.

- Finally, the placebo group reported more adverse events (8 subjects with 10 events), compared with the ketorolac group (3 patients with 3 events). Headache was the only adverse event in the ketorolac group.
In summary, a single dose of IN ketorolac 31.5 mg was well tolerated and effectively managed postoperative pain in oral surgery patients for up to 8 hours.
"Intranasal Ketorolac for Postoperative Pain: A Phase 3, Double-Blind, Randomized Study"

• Following major surgery, primarily hysterectomies and hip replacements

• Patients receiving ketorolac IN had superior quality of analgesia ratings and significant reduction in morphine use compared to those receiving placebo IN

• Nasal irritation occurred more frequently with ketorolac than with placebo (24% vs 2%).

• Conclusion: ketorolac IN well tolerated and effective in treating moderate-to-severe postoperative pain.
"Intranasal Ketorolac for Acute Postoperative Pain"

- Mean of summed pain intensity difference scores at 6 hours were significantly greater in the ketorolac group, indicating better analgesic efficacy compared to placebo (117.4 vs 89.9)

- Pain intensity difference indicated significantly better pain relief in the ketorolac group at 20 minutes after the first dose

- Morphine use over 48 hours decreased 26% in the ketorolac group compared to placebo

- Global pain control scores on day 1 were significantly higher in the ketorolac group compared to placebo

- Adverse events and serious adverse event incidences were similar in both groups (Rhinalgia and nasal irritation occurred more frequently with ketorolac)

- The conclusion of the study was ketorolac nasal spray was well tolerated and provided effective pain relief within 20 minutes with reduced opioid analgesic use.
Pharmacokinetics of IN ketorolac were similar to those following IM administration.

Ketorolac was administered to 15 healthy volunteers using single doses of the drug and a cross-over design. Subjects received open-label randomized 15- and 30- mg intramuscular (I.M.) ketorolac and blinded randomized 15- and 30- mg intranasal (I.N.) ketorolac after appropriate washout periods.

Ketorolac IN was rapidly and well absorbed with a half-life of 5-6 hours which was similar to the values after I.M. administration. The bioavailability of ketorolac nasal spray dose was 75% compared to the bioavailability after the I.M. dosing. The only nasal symptoms were some instances of mild irritation.
Ketorolac Nasal Spray (Sprix®)

- Pharmacologic Category: Nonsteroidal Anti-inflammatory Drug (NSAID), Nasal
- Use: Short-term (≤5 days) management of moderate-to-moderately-severe acute pain requiring analgesia at the opioid level
- Effects on Dental Treatment: Nasal discomfort, rhinalgia, throat irritation
Ketorolac Nasal Spray (Sprix®)

- NSAIDs are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin.
- Platelet function is restored as the drug is eliminated from the body.
- No evidence to warrant discontinuance of NSAIDs prior to dental surgery.
- If therapy is continued without interruption, the clinician should anticipate the potential for slower clotting times.
One issue that often presents is the recovering narcotic addict undergoing dental surgery and requiring effective post-surgical pain relief.

Narcotic pain relievers would be contra-indicated.

Ketorolac nasal spray would seem to be a good choice in managing pain in these patients.

Sprix®: 15.75 mg/spray (1.7 g)

<65 years and ≥50 kg: One spray (15.75 mg) in each nostril (total dose: 31.5 mg) every 6-8 hours; maximum dose: 4 doses (126 mg)/day.
A total of 234 patients were randomly assigned to treatment and included in the intent-to-treat population.

Sum of pain relief and pain intensity differences, the group receiving the combination of ibuprofen 400 mg/acetaminophen 1000 mg had significantly better mean scores compared with ibuprofen 400 mg alone, acetaminophen 1000 mg alone and the combination of ibuprofen 200 mg/acetaminophen 500 mg.

Sum of pain relief and pain intensity differences, the group receiving the combination of ibuprofen 200 mg/acetaminophen 500 mg had significantly better mean scores compared with acetaminophen 1000 mg alone, but not compared to ibuprofen 400 mg alone.

Results for secondary endpoints

Ibuprofen 400 mg/acetaminophen 1000 mg was associated with significantly better scores than was single agent therapy for total pain relief, sum of pain intensity differences, sum of pain intensity differences on the visual analog scale at all time intervals, and for sum of pain relief and pain intensity differences from 4 to 6 hours.
Mean Pain Relief and Intensity Differences

- Ibuprofen 400 mg/paracetamol 1000 mg
- Ibuprofen 200 mg/paracetamol 500 mg
- Ibuprofen 400 mg
- Paracetamol 1000 mg
- Placebo

Time (min)

0 30 60 90 120 180 240 300 360 420 480

James L. Rutkowski DMD, PhD
FDA Limits Acetaminophen in Prescription Combination Pain Relievers to 325 mg

- FDA is asking manufacturers of prescription combination products that contain acetaminophen to limit the amount of acetaminophen to no more than 325 mg/tablet or capsule

- FDA is also requiring manufacturers to update labels of all prescription combination acetaminophen products to warn of the potential risk for severe liver injury.
### VICODIN® (hydrocodone bitartrate and acetaminophen tablets, USP)

- **5 mg/500 mg**
- **Usual adult dose:** See package insert.
- **Caution:** Federal law prohibits dispensing without a prescription.
- **Storage:** 59°F-86°F (15°C-30°C). Dispense in tight, light-resistant container as defined in the USP.

### Generic Name Table

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<th>Brand name</th>
<th>Generic name</th>
<th>Form</th>
<th>Strength</th>
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<tbody>
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<td>Acetaminophen/codeine phosphate</td>
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<td>500/5 mg</td>
</tr>
</tbody>
</table>

### LORCET® PLUS (hydrocodone bitartrate and acetaminophen tablets USP)

- **7.5 mg/650 mg**

### PERCOCET (oxycodone and acetaminophen tablets, USP)

- **10 mg / 325 mg**
- **20 mg / 650 mg**

### LORTAB® (hydrocodone bitartrate, acetaminophen, USP)

- **2.5 mg / 500 mg**
- **5 mg / 500 mg**
- **7.5 mg / 500 mg**
- **10 mg / 500 mg**
Drug effects on Bone

James L. Rutkowski DMD, PhD
The Effects of Medications on Bone
Stuart B. Goodman, William Jiranek, Edward Petrow, and Alan W. Yasko

- NSAIDs
- Anticoagulants
- Antacids
- Bisphosphonates
- Corticosteroids
- Anti-neoplastic
- Antiepileptic
- Disease-Modifying Antirheumatic Drugs (DMARDs)
Disease-Modifying Anti-rheumatoid Drugs (DMARDS)

- Methotrexate (MTX) (Trexall™)
- Cyclosporine (Gengraft™)
- Leflunomide (Arava™)
- Anti-tumor necrosis factor-α (TNF-α) (Intron® A)
- Anti-interleukin-1 (IL-1) (Kineret®)

Used singly or in combination with other drugs
Methotrexate (MTX) (Trexall™)

• Folic acid antagonist

• Causes a dose-dependent ↓ osteoblast proliferation (although may not be significant at lower doses used to Tx rheumatoid arthritis)
Methotrexate (MTX) (Trexall™)

- Effects on Dental Treatment:

  - Ulcerative stomatitis, gingivitis, glossitis, and mucositis (dose dependent; appears 3-7 days post-therapy and resolves within 2 weeks)

- NSAIDS concurrent administration may cause severe bone marrow suppression, aplastic anemia, and GI toxicity

  - Risk is lower at the methotrexate dosages used for rheumatoid conditions/psoriasis, the addition of an NSAID or salicylate may still lead to unexpected toxicities;
Methotrexate (MTX) (Trexall™)

● Bleeding effects

● Chemotherapy may result in significant myelosuppression, potentially including significant ↓ in platelet counts and altered hemostasis

● Risk of thrombocytopenia is low with dosages used in rheumatoid management
Cyclosporine (Gengraft™)

- Cyclic fungal peptide that inhibits the activation of T-lymphocytes
  - inhibits the transcription of the IL-2 gene
  - used in rheumatoid arthritis and prevention of organ rejection
  - ↑ osteoclast-mediated bone resorption exceeds bone formation
- Low dose not much of a problem
Cyclosporine (Gengraft™)

- Effects on Dental Treatment
  - Mouth sores, swallowing difficulty, gingivitis, gum hyperplasia, xerostomia (normal salivary flow resumes upon discontinuation), abnormal taste, tongue disorder, tooth disorder, and gingival bleeding.
Leflunomide (Arava™)

- Inhibits pyrimidine biosynthesis → inhibits T cell proliferation and activation
- Inhibits osteoclastogenesis and osteoclast function

Effects on Dental Treatment
- Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, oral candidiasis, abnormal taste, tooth disorder, enlarged salivary gland, esophagitis, and gingivitis.

Bleeding effects:
- Associated with rare thrombocytopenia
Anti-tumor necrosis factor-α (TNF-α) (Intron® A)

- **Effects on Dental Treatment**
  - Xerostomia (normal salivary flow resumes upon discontinuation), metallic taste, taste alteration, and gingivitis.

- **Bleeding effects**
  - Chemotherapy may result in significant myelosuppression, potentially including significant reduction in platelet counts and altered hemostasis. In patients who are under active treatment with these agents, medical consult is suggested.
Psychotropic Drugs

- Neuroleptic medication (schizophrenia) → hyperprolactinemia → decreased bone density

- 1st generation
  - Phenothiazines (Thorazine, Trilafon, Stelazine, Melleril, Phenergan)

- 2nd generation
  - Clozapine, Seroquel

- 3rd generation
  - Abilify
Psychotropic Drugs

- antidepressants
  - Imipramine = ↑ density
  - SSRIs = no change

- Lithium = ↑ secretion of parathyroid hormone ⇒ ↓ BMD (?)

- Recommendation:
  - Therapy (> 1 year) perform BMD studies yearly
  - Calcium 1,500 mg/day
  - Vitamin D 400-800 IU/day
Anti-epileptic Drugs (AEDs)

- Induce cytochrome P-450 enzymes = affect bone metabolism
  - $\uparrow$ catabolism of vitamin D = $\downarrow$ bioavailability of vitamin D
  - impaired calcium absorption
  - alterations in bone formation and degradation
  - $\uparrow$ PTH release
- abnormalities in calcitonin or Vitamin K
- Hypocalcemia, hypophosphatemia
  - Phenytoins (Dilantin)
  - Phenobarbital
  - Carbamazepine (Tegretol ®)
  - Valproate disodium (Depakote®)
Vitamin K

- ↓ vitamin K = ↑ bone fractures
- warfarin (Coumadin®) induces ↓ vitamin K
- OsteoK ® (Vitamin D3, Vitamin K2, Calcium)
Statins

- Atrovastatin (Lipitor®), Fluvastatin (Lescol®), Lovastatin (Mevacor®), Mevastatin (Compactin®), Pravastatin (Pravachol®), Dosuvastatin (Crestor®), Simvastatin (Zocor®)

- Prevent cardiovascular events
  - ↓ production of cholesterol and low-density lipoproteins,
    ↑ coronary vasodilation, ↓ inflammation
  - ↑ BMP-2 release by osteoblasts
  - ↓ osteoclast differentiation
  - ∴ increase BMD
Antacids

- Phosphorus essential for bone formation

- Aluminum-containing antacids bind phosphate \( \therefore \) cannot be absorbed from the gut

- lead to hypophosphatemia = metabolic bone disease
Glucocorticosteroids

- Dexamethasone (Decadron®)
- Prednisone
- Methylprednisolone (Medrol®)

Bone effects

- Suppression of intestinal calcium absorption
- ↓ renal tubular calcium reabsorption
- ↑ urinary calcium excretion
Glucocorticosteroids

- Suppressed osteoblast function = ↓ bone formation
- ↑ parathyroid secretion
- ↓ estrogen and testosterone = bone resorption
- promote apoptosis of osteoblasts and osteocytes
- ↑ production of RANKL = ↑ osteoclasts
Role of corticosteroids on the OPG/RANKL/RANK system of bone metabolism. In bone, osteoblasts and their precursors (stromal cells) express a cell-bound and soluble form of receptor activator of nuclear factor κB ligand (RANKL) as well as the soluble neutralizing receptor, osteoprotegerin (OPG). Under permissive levels of macrophage colony-stimulating factor (M-CSF), binding of osteoblast-derived RANKL to the receptor activator of nuclear factor κB (RANK) induces differentiation of osteoclast precursors to multinucleated osteoclasts. Once mature, osteoclast apoptosis is induced by OPG, and prevented by RANKL. By decreasing OPG production and increasing RANKL expression, corticosteroids enhance osteoclast formation and longevity.
Glucocorticosteroids

• Long-term chronic use ↓ COX-2 expression and therefore PG production

• Result: Bone loss
# Medications for Arthritis

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<th>Effect Description</th>
<th>Score</th>
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<td><strong>NSAIDs</strong></td>
<td>Inhibits Cox 1 &amp; 2 enzymes</td>
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<tr>
<td></td>
<td>Inhibits fracture healing and bone growth - reversible with D/C of drug</td>
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<tr>
<td></td>
<td>Score = -1</td>
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<tr>
<td><strong>Methotrexate</strong></td>
<td>High Doses: Interferes with osteoblast proliferation</td>
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<td>Low Doses: May be anti-inflammatory</td>
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<td>Anti-rheumatoid dose of 10 mg/wk does not interfere with bone</td>
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<td>Score = 0</td>
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<td><strong>Cyclosporin</strong></td>
<td>Inhibits activation of T-Lymphocytes</td>
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</tbody>
</table>
## Medications for Arthritis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect and Function</th>
<th>Overall Effect on Bone</th>
<th>Score</th>
</tr>
</thead>
</table>
| Leflunomide                 | 1. Inhibits pyrimidine biosynthesis  
2. Inhibits T cell proliferation and activation  
3. Inhibits osteoclastogenesis and osteoclast function | Clinically unknown     | Undecided |
| Anti-TNF-α and anti-IL-1 drugs | Inhibit inflammatory cytokines that normally upregulate osteoclastogenesis and suppress osteoblast function | Clinical studies inconclusive | Undecided |

Net score = -1

0 x 2

Undecided x 2
## Commonly Prescribed Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effects</th>
<th>Potential Side Effects</th>
</tr>
</thead>
</table>
| **Bisphosphonates**| 1. Interfere with osteoclast recruitment and function  
2. ↑ osteoclast apoptosis | 1. Inhibit bone resorption  
2. Improve BMD and fracture risk  
3. Long term = negative effects |
| **Antiepileptics** | Affect the cytochrome P-450 enzyme pathway, which adversely affects Vitamin D-PTH - calcitonin axis | 1. May lead to rickets and osteomalacia  
2. Requires monitoring of vitamin D, Calcium, Phosphorus |
# Commonly Prescribed Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
<th>Net Score</th>
</tr>
</thead>
</table>
| **Statins**                         | 1. Inhibit production of mevalonate  
2. ↑ BMP-2 release by osteoblasts  
3. ↓ osteoclast differentiation | 1. Improve BMD  
2. ↓ fracture risk of hip |
| **Aluminum-containing antacids**    | Bind phosphate in the gut                                               | In excess, may lead to hypophosphatemia, rickets, and osteomalacia |

Net Score = 1 + 2 - 1+/-
# Cancer Treatment - Induced Bone Loss

<table>
<thead>
<tr>
<th>Direct:</th>
<th>Indirect:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antineoplastic agents:</td>
<td></td>
</tr>
<tr>
<td>• Methotrexate</td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>• Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>• Ifosamide</td>
<td></td>
</tr>
<tr>
<td>• Glucocorticosteroids</td>
<td></td>
</tr>
<tr>
<td>• Prednisone</td>
<td></td>
</tr>
<tr>
<td><strong>↓</strong> bone formation 2° to effects on osteoblast and osteoclast activity</td>
<td></td>
</tr>
</tbody>
</table>

| Selective estrogen receptor modulators |
|• Tamoxifen |
|• Toremifene |
|• Raloxifene |

**Act as an estrogen antagonist at β receptors**

**Suppress osteolast/bone formation**
### Cancer Treatment - Induced Bone Loss

<table>
<thead>
<tr>
<th>Indirect:</th>
<th>Inhibit enzymatic conversion of adrenal androgens to estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitors</td>
<td></td>
</tr>
<tr>
<td>• Anastrozole</td>
<td></td>
</tr>
<tr>
<td>• Letrozole</td>
<td></td>
</tr>
<tr>
<td>• Exemestane</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect:</th>
<th>Inhibit release of follicle-stimulating hormone and leuteinizing hormone resulting in chemical castration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotropin-releasing hormone analogs (agonists)</td>
<td></td>
</tr>
<tr>
<td>• Leuprolide</td>
<td></td>
</tr>
<tr>
<td>• Goserelin</td>
<td></td>
</tr>
<tr>
<td>• Triptorelin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect:</th>
<th>Androgen receptor antagonist; lowers circulation testosterone and estradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiandrogens (steroidal)</td>
<td></td>
</tr>
<tr>
<td>• Cyproterone</td>
<td></td>
</tr>
</tbody>
</table>


## Cancer Treatment - Induced Bone Loss

<table>
<thead>
<tr>
<th>Indirect:</th>
<th>Competitive inhibitors of androgen receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiandrogens (nonsteroidal)</td>
<td>Cause ovarian insufficiency</td>
</tr>
<tr>
<td>• Flutamide</td>
<td>Suppress osteoblasts/bone formation</td>
</tr>
<tr>
<td>• Bicalutamide</td>
<td></td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td></td>
</tr>
<tr>
<td>• Mechlorethamine</td>
<td></td>
</tr>
<tr>
<td>• Vincristine</td>
<td></td>
</tr>
<tr>
<td>• Procarbazine</td>
<td></td>
</tr>
<tr>
<td>• Cyclophosphamide</td>
<td></td>
</tr>
</tbody>
</table>

Net Score = 21 -
Epinephrine Key Drug Interactions

James L. Rutkowski DMD, PhD
## Selected Adrenergic Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpha</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+</td>
</tr>
<tr>
<td>Levonordefrin</td>
<td>+</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>+</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>O</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>+</td>
</tr>
<tr>
<td>Albuterol</td>
<td>O</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>O</td>
</tr>
</tbody>
</table>
Non-Specific Beta Blockers

• Treatment

  Angina     Dysrhythmia

  Tremors    Glaucoma

  Hypertension   Migraine

  M.I.     Pheochromocytoma
Non-Specific Beta Blockers

- Competitively block stimulation of beta receptors by Epi and Norepi
Types of Beta Blockers

- Non-selective
  - Propranolol - Rx Inderal
  - Nadolol - Rx Corgard

- Selective
  - Selective B-1
  - Atenolol - Rx Tenormin
  - Metoprolol - Rx Lopressor
Non-Selective Beta Blockers with Epi

- Massive unopposed alpha vasoconstriction
- Hypertensive crisis
- Significance rating 1
COMT Inhibitors

- A New Drug Interaction?
COMT Inhibitors
CATECHOL-O-METHYL TRANSFERASE

• COMT Inhibitors
  • Tolcapone (Rx Tasmar)
  • Entacapone (Comtan)

• Tx Parkinson’s Disease
Catechol-O-Methyl-Transferase

- Enzyme responsible for inactivating catechols
  - levodopa
  - vasoconstrictors
    - epinephrine
    - levonordefrin
COMT Inhibitors with Epi

400 mg of Entacapone + Epinephrine

Tachycardia
COMT Inhibitors with Epi Reasonable Precaution

One carpule of 1:100,000 epinephrine and monitor patient’s B.P. and pulse for 5 minutes
COMT Inhibitors with Epi Patients at Risk

- Low COMT activity
- Selegiline - Rx Eldepryl
  - specific (MAO)-B inhibitor
  - high doses block (MAO)-A also
  - both pathways for epinephrine metabolism are blocked
COMT Inhibitors with Epi

• Significance rating 1

• Also unique to Tolcapone is acute liver failure - watch Tylenol
Monoamine Oxidase Inhibitors

- Antidepressants
  - Marplan and Parnate

- Antimicrobial
  - Furazolidone - Rx Furoxone

- Antiparkinson
  - Selegiline - Rx Eldepryl
MAO Inhibitors

• Prevent metabolism of drugs metabolized by MAO

• Block intraneuronal breakdown of norepinephrine, increases the pool of neurotransmitter capable of being released by amphetamine, pseudoephedrine and tyramine
MAO Inhibitors with Epi

• No evidence of problem with epi or levonordefrin - reason COMT

• Bureaucracy?
MAO Inhibitors

- Remember Sudafed and MAO - sinus elevations
- Remember MAOI’s and Meperidine - Rx Demerol
  - Muscle rigidity, stupor, agitation, increased temperature, hallucinations, death (?) Talwin, Nubain
TCA with Epi

- Block active reuptake of amine neurotransmitters
- Get potentiation of affected neurotransmitter
- Epi subject to same affects
Tricyclic Antidepressants

- Imipramine - Rx Tofranil
- Amitriptyline - Rx Elavil
- Doxepin - Rx Sinequan

Tx: depression, anxiety, neuropathic pain, nocturnal enuresis
TCA with Epi
Boakes Found

- Increase in systolic B.P.
- Dysrhythmia
TCA with Epi

- Tofranil potentiates epi 3 X
- Potentiates Levonordefrin 6-8 X
TCA with Epi
Persson and Siwers 1975

- 2 1/2 Carpules of Lido 2% with Epi 1:100,000
  - causes headache
  - increased systolic pressure 45 mm Hg over baseline
TCA with Epi
Brown and Lewis in 3-0 1988

- Prolonged use of TCA's
  - desensitization to adrenergic vasoconstrictors
  - decrease chance of interaction significance
TCA with Epi
Treatment Plan

• No levonordefrin

• no epi cord

• no greater 1:100,000 epi

• 1/3 maximum dose

• wait 30 minutes before re-injecting
TCA with Vasoconstrictor

• Significant rating is a 1
Thyroid Hormones and Vasoconstrictors

- Thyroxine - Rx Synthroid
- May cause dysrhythmias, ↑ cardiac output, ischemia
- Significance rating 4
Cocaine

- Has L.A. action
- Blocks the re-uptake of norepi and dopamine
- Enhances adrenergic neurotransmitter release
Cocaine with Epi
Treatment Plan

• Discontinue Cocaine use at least 24 hours prior to dental appointment
Efficacy of Articaine: Amide Local Anesthetic

- Articaine 4% with Epi 1:100,000 vs. Xylo 2% with Epi 1:100,000
- 882 received Articaine
- 443 received Xylocaine
- No difference between two groups

Ref. JADA, May 2000
Articaine vs. Citanest Forte

Articaine 4% with Epi 1:200,000 found to be no different than Citanest Forte (Epi 1:200,000)

Articaine

- Same recommended maximum dose as Xylocaine 7 mg per Kg.

- Formulation is twice as strong - WHY?
Articaine

- Has epi 1:100,000 - ? Mandibular blocks
- Prilocaine (Citanest Epi 1:200,000)
  - lower recommended dose

WHY?
TOP 10 THINGS TO KNOW ABOUT

DRUGS IN DENTISTRY

James L. Rutkowski, D.M.D., Ph.D.
# 10

- STEROIDS AND NSAIDS ARE A DENTIST’S BEST FRIEND
  – BECAUSE IT CAN MAKE YOU LOOK GOOD, EVEN IF YOUR NOT
#9

- NSAIDS AND ANTIHYPERTENSIVES CAN LEAD TO INCREASED BLOOD PRESSURE (FOR BOTH YOU AND THE PATIENT) – BECAUSE OF A DRUG INTERACTION
#8

- EPINEPHRINE IS OK IN A PATIENT WITH CONTROLLED CARDIOVASCULAR DISEASE – BUT YOU MUST KNOW WHAT YOU ARE DOING
  - ALWAYS HAVE A BASELINE PULSE AND BP
#7

- NSAIDs can destroy your bone grafts
- Especially Cox-2 specific
- STOP the Cox-2 before it stops you!!
- Flurbioprofen - New Best Friend
#6

- EPINEPHRINE WITH INDERAL OR CORGARD (or high dose selective β-1 blockes) CAN LEAD TO A BAD DAY – HYPERTENSIVE CRISIS
#5

- ACETAMINOPHEN IN THE ALCOHOLIC
  - KEEP HIM DRINKING, THIS ISN’T THE TIME TO QUIT!
#4

- COUMADIN – IF YOU KNOW HOW TO WORK WITH IT, ITS OK TO SEE RED
- KNOW THE PATIENT’S
  - TARGET INR
  - CURRENT INR
  - RISK OF YOUR PROCEDURE
- KNOW YOUR STUFF AND YOUR COMFORT LEVEL
#3

- DIABETICS NEED DENTAL TREATMENT TOO
  - KNOW HOW TO DEAL WITH THEIR INSULIN AND HYPOGLYCEMIC AGENTS – LET’S EAT
#2

- **ANTIBIOTICS**
  - HAVE A SOUND PROTOCOL FOR THEIR USE
    - DO NOT OVERUSE
    - KNOW WHEN TO USE
    - KNOW HOW TO USE
  - WORK BEST WITH MOIST HEAT!
#1

**KNOW YOUR PATIENT**

- **VALID MEDICAL HISTORY**
  - REVIEWED EVERY APPT. (This is how they will get to know you too)

- **BASELINE VALUES**
  - BLOOD PRESSURE
  - PULSE

- THIS IS #1
TAKE-HOME MESSAGE

“Through diligence, moral clarity, ingenuity and a simple willingness to try, better is possible!”
– Better by Atul Gawande - 2007
Glucocorticosteroid

• USE IN DENTISTRY
During therapy:

- Prescribe drug with food
- Diet low in calories and sodium and rich in potassium
- Check periodically for weight gain, hypertension, hyperglycemia
Rule of 2’s

- Adrenocortical suppression should be suspected if a patient has received Glucocorticoid therapy
  - In a dose of 20 mg or more of cortisone or its equivalent daily
    - Via oral or parenteral route or a continuous period of 2 weeks or longer within 2 years of the dental appointment
  - Ref. Medical emergencies in dental office, Stanley F. Malamed
  - Complications in Anesthesia - John L. Atlee; Page-132
### Protocol for Supplementation of Patients on Glucocorticoid Therapy Who Are Undergoing Dental Care (Burket's 10th ed)

<table>
<thead>
<tr>
<th>Dental Procedure</th>
<th>Previous Systemic Steroid Use</th>
<th>Current Systemic Steroid Use</th>
<th>Daily alternating Systemic Steroid Use</th>
<th>Current topical Systemic Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine procedures</td>
<td>If prior usage lasted for &gt; 2 weeks and ceased &lt; 14–30 days ago, give previous maintenance dose</td>
<td>No supplementation needed</td>
<td>Treat on steroid dosage day; no further supplementation needed</td>
<td>No supplementation needed</td>
</tr>
<tr>
<td></td>
<td>If prior usage ceased &gt; 14–30 days ago, no supplementation needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Procedure</td>
<td>Previous Systemic Steroid Use</td>
<td>Current Systemic Steroid Use</td>
<td>Daily alternating Systemic Steroid Use</td>
<td>Current topical Systemic Steroid Use</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Routine procedures</td>
<td>If prior usage lasted for &gt; 2 weeks and ceased &lt; 14–30 days ago, give previous maintenance dose</td>
<td>No supplementation needed</td>
<td>Treat on steroid dosage day; no further supplementation needed</td>
<td>No supplementation needed</td>
</tr>
</tbody>
</table>

*If prior usage ceased > 14–30 days ago, no supplementation needed*
<table>
<thead>
<tr>
<th>Dental Procedure</th>
<th>Previous Systemic Steroid Use</th>
<th>Current Systemic Steroid Use</th>
<th>Daily alternating Systemic Steroid Use</th>
<th>Current topical Systemic Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extractions, surgery, or extensive procedures</td>
<td><em>If prior usage lasted &gt; 2 weeks and ceased &lt; 14–30 days ago, give previous maintenance dose</em></td>
<td><em>Double daily dose on day of procedure</em></td>
<td><em>Treat on steroid dosage day, and give double daily dose on day of procedure</em></td>
<td><em>No supplementation needed</em></td>
</tr>
<tr>
<td></td>
<td><em>If prior usage ceased &gt; 14–30 days ago, no supplementation needed</em></td>
<td><em>Double daily dose on first postoperative day when pain is anticipated</em></td>
<td><em>Give normal daily dose on first postoperative day when pain is anticipated</em></td>
<td></td>
</tr>
</tbody>
</table>
Patient requiring extractions took a 7 day course of 20 mg. of prednisone for exacerbation of asthma one week ago.

No supplementation required. Even though the dose was suprarephysiologic, the course of time it was taken was less than 2 weeks.
Scenario Two

Patient requiring extractions is taking 10 mg of prednisone for the past year to treat rheumatoid arthritis.

This patient’s HPA axis is probably suppressed due to supraphysiologic dose of corticosteroids for longer than 2 weeks. Supplement with at least 100 mg of cortisol equivalent (25 mg prednisone) in the morning on the day of the surgery.
INFLAMMATION

- VASCULAR & CELLULAR IS A PROTECTIVE MECHANISM
- ANTI-INFLAMMATORY MEDS.
- INTERRUPT SYNTHESIS AND/OR RELEASE OF MEDIATORS OF THE VASCULAR RESPONSE
PHYSIOLOGICAL ASPECTS

• CORTISOL (STEROIDAL HORMONE)
  • RELEASED BY ADRENAL CORTEX
  • REGULATES GLUCOSE METABOLISM
  • HENCE GLUCOCORTICOSTEROIDS
ADRENAL CORTEX

- UNDER CONTROL OF HYPOTHALAMUS

- HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

- “HPA AXIS”
# Steroid Effects

<table>
<thead>
<tr>
<th>Physiological Effects</th>
<th>Adverse Effects Associated With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid Actions:</td>
<td></td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Potentiate catecholamines</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Inhibit erythropagocytosis</td>
<td>Polycythemia</td>
</tr>
<tr>
<td>Inhibit production of lymphocytes &amp; monocytes</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Mineralcorticoid Actions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Edema, Hypertension</td>
</tr>
<tr>
<td>Poorly understood functions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoporosis, myopathy, peptic ulcer, fat redistribution, psychological changes</td>
</tr>
</tbody>
</table>
ANTI-INFLAMMATORY ACTION

- SUPRAPHYSIOLOGICAL DOSES
- MECH. OF ACTION
  - DECREASE IN INFLAMMATORY MEDIATORS
  - SYNTHESIZE AN ENZYME THAT DEGRADES BRADYKININ
IMMUNOSUPPRESSANT EFFECTS

- ANTIBODY PRODUCTION ↓ BY LARGE STEROID DOSE, NOT MODERATE DOSE
- RETARD LYMPHOCYTE ACTIVITY
- STEROIDS ↑ MIGRATION OF ANTI-INFLAMMATORY MONOCYTES TO SITES OF INFECTION
STEROIDS - THE BAD SIDE

- CHRONIC STEROID THERAPY
  - SUPPRESSION OF HPA AXIS
  - COMPROMISED IMMUNE STATUS
  - OSTEOPOROSIS
  - INCREASED BLOOD SUGAR LEVELS
How does stress induce ↑ Corticosteroid production?

- At the hypothalamus, fear-signaling impulses activate both the sympathetic nervous system and the modulating systems of the HPA axis.

- E/NE will positively feedback to the pituitary and increase the breakdown of POMCs (Pro-opiomelanocortin) into ACTH

![Diagram of Pro-opiomelanocortin (POMC) metabolism](image)
• Increase dose in case of stress
• Instruct patient not to stop abruptly

• When stopping therapy:
  • Taper dose
ADDITIONAL STEROIDS

• IF PATIENT TAKES DAILY STEROIDS:

  • DOUBLE OR TRIPLE THERE DAILY DOSE FOR THE DAY OF SURGERY
  
  • TAPER OFF OVER THE NEXT 2 DAYS TO NORMAL DOSE

  • OR GIVE IV SHORT ACTING STEROIDS AND LONGER ACTING IM SUSPENSION STEROIDS
Precautions before administering glucocorticosteroids

- Ask and check for hypertension, diabetes mellitus, peptic ulcer, infection, psychosis
Relative Contraindications

- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Pregnancy
- Herpes simplex keratitis
- Tuberculosis
- Osteoporosis
- Psychosis
- Epilepsy
- Renal failure
CYP3A4

• Dexamethasone is a strong inducer of CYP3A4

• Dexamethasone is a substrate of CYP3A4

• Benzodiazepines are substrates of CYP3A4
Glucocorticosteroids

- “A SINGLE DOSE OF GLUCOCORTICOID, EVEN A LARGE ONE, IS VIRTUALLY WITHOUT HARMFUL EFFECTS, AND A SHORT COURSE OF THERAPY (UP TO 1 WEEK), IN THE ABSENCE OF SPECIFIC CONTRAINDICATIONS, IS UNLIKELY TO BE HARMFUL”

- GOODMAN & GILLMANS – 10TH EDITION
STEROIDS

• ALL EQUIPOTENT

• VARY IN

• POTENCY

• HALF-LIFE

• MINERALCORTICOID ACTIVITY

• SALT RETENTION – FLUID RETENTION
DENTAL APPLICATIONS

- SURGERY
  - PRE-OPERATIVE
    - PREVENT INFLAMMATION (SWELLING)
- TRAUMATIC OR APHTHOUS ULCERS
- NEURITIS OF INFERIOR ALVEOLAR OR MENTAL NERVES
- PHELBITIS FROM IV SEDATION
STEROID EFFECT ON INFERIOR ALVEOLAR NERVE HYPERSENSITIVITY

• 14 PATIENTS
• 3rd MOLAR REMOVAL
• DEXAMETHASONE/DIPYRONE VS DIPYRONE ALONE

• DIPYRONE ONLY PTS. HAD SIGNIFICANTLY REDUCED LINGUAL AND INFERIOR ALVEOLAR NERVE ELECTRICAL DETECTION THRESHOLDS 2 DAYS AFTER SX

• PTS RECEIVING DEXAMETHASONE HAD NO SIGNIFICANT REDUCTION IN ELECTRICAL DETECTION THRESHOLD

• J. ORAL FAC. PAIN 2004 Barron RP et al
STEROID REGIMEN

• ORAL – USE THE DOSE PAKS AVAILABLE (MEDROL DOSE PAK)

• PT. TAKES ALL OF THE FIRST ROW IN THE AM PRIOR TO SURGERY (OR SPLITS DOSE – ½ IN AM AND ½ EARLY AFTERNOON)

• THEN FOLLOW DIRECTIONS FOR FOLLOWING DAYS
Decadron®
DEXAMETHASONE

Elixir
0.5 mg per 5 ml

Alcohol 5%
Benzoic acid, 0.1% added as preservative.

Manufactured in Zouk Mosbeh, Lebanon, by
ALGORITHM S.A.L.
Formulated / packaged using know-how obtained from Merck & Co. Inc.
© Registered Trademark
STEROID REGIMENS

- **IV OR IM**
  - USE DEXAMETHASONE SODIUM PHOSPHATE 4mg/ml (SOLUTION – CLEAR)
  - GIVE 4 – 8 mg IV OR IM PRIOR TO SURGERY
    - LASTS 24 - 48 HRS.
  - OR USE SOLU-CORTEF 100 mg IM OR IV
    - LASTS 24 – 36 HRS.
STEROID REGIMENS

- IM FOR LONGER DURATION
  - DEXAMETHASONE LA 8 mg/ml
    - SUSPENSION (WHITE) GIVE 1 ML
  - OR DEPO-MEDROL 40 mg/ml
    - SUSPENSION (WHITE) GIVE 1 –2 ml
  - THESE WILL LAST 5 TO 7 DAYS
  - NEVER GIVE SUSPENSIONS IV
Depo-Medrol™
Sterile aqueous suspension
80 mg
Methylprednisolone acetate
2 ml
FOR INTRAMUSCULAR, INTRA-ARTICULAR AND SOFT TISSUE INJECTION
Betamethasone sodium phosphate and Bethamethasone acetate Suspension

Contains both short acting and long acting betamethasone

FOR IM USE ONLY

Give 1 -2 mL IM
CONTRAINDICATIONS
(even short term use)

• UNCONTROLLED DIABETES
• IMMUNOCOMPROMISED
• ACTIVE PEPTIC ULCER
• OSTEOPOROSIS
• ACTIVE HERPETIC OR FUNGAL INFECTIONS
• AVOID HIGH DOSE IN PTS. WITH PSYCHOSES
Conclusion

• Corticosteroids play an important role in control of pain & inflammation associated with numerous disease states of oral cavity.

• Currently corticosteroids are drugs with one of the broadest spectrum of clinical utility.

• But it should never be used as a substitute to other treatments.

• Lets keep it mind that these drugs do not cure the disease but rather control or relieve the symptoms.

• It should be used cautiously as it is two edged sword
## Steroid doses (Injection) - Guidelines

**DOSES MUST BE INDIVIDUALIZED FOR EACH PATIENT AND A CONSULTATION WITH THE PATIENT’S HEALTH CARE PROVIDER MAY BE INDICATED**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dexamethasone Sodium Phosphate (IV or IM) Clear Solution</th>
<th>Depo-Medrol (IM only) white suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single implant small flap</td>
<td>2-4 mg</td>
<td>10-20 mg or none</td>
</tr>
<tr>
<td>Single implant med flap</td>
<td>4 to 6 mg</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Multiple implants large flap</td>
<td>6 to 8 mg</td>
<td>40-60 mg</td>
</tr>
<tr>
<td>Full arch flap with multiple implants</td>
<td>8 mg</td>
<td>60 to 80 mg</td>
</tr>
</tbody>
</table>
Steroid doses (Oral) Guidelines

**DOSES MUST BE INDIVIDUALIZED FOR EACH PATIENT AND A CONSULTATION WITH THE PATIENT’S HEALTH CARE PROVIDER MAY BE INDICATED**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Dexamethasone 0.75 mg tablets</th>
<th>Number of Prednisone 5 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1  Day 2  Day 3  Day 4  Day 5  Day 6  Day 7</td>
<td>Day 1  Day 2  Day 3  Day 4  Day 5  Day 6  Day 7</td>
</tr>
<tr>
<td>Single implant small flap</td>
<td>4  3  2  1  none  none  none</td>
<td>4  3  2  1  none  none  none</td>
</tr>
<tr>
<td>Single implant med flap</td>
<td>5  4  3  2  1  none  none</td>
<td>5  4  3  2  1  none  none</td>
</tr>
<tr>
<td>Multiple implants large flap</td>
<td>6  5  4  3  2  1  none</td>
<td>6  5  4  3  2  1  none</td>
</tr>
<tr>
<td>Full arch flap multiple implants</td>
<td>7  6  5  4  3  2  1</td>
<td>7  6  5  4  3  2  1</td>
</tr>
</tbody>
</table>
CONTRAINDICATIONS
(even short term use)

• DIABETES
• Pregnancy
• IMMUNOCOMPROMISED
• ACTIVE PEPTIC ULCER
• OSTEOPOROSIS
• ACTIVE HERPETIC OR FUNGAL INFECTIONS
• AVOID HIGH DOSE IN PTS. WITH PSYCHOSES
Get the slides (PDFs)

- Check email Monday afternoon (August 31, 2015)
  - Login and password will be provided
  - If no email: Call Dustin 1-814-226-6390

- Content information contact
  - Jim Rutkowski
    - email: jim@rutkowskidmdphd.com
    - phone: (office) 1-814-226-8690
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