

Management of Ocular Pain and Inflammation



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A CLINICAL MOMENT:

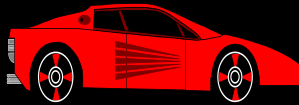
80 y/o with severe temporal headache presents to ER

**ER DX: Migraine
TX with Midrin**

Classical Migraine Symptoms? What IS the Differential?

NOT the Rear-end of An Automobile

- Do the facts support the DX?
- What is the Differential DX?
- Will this TX produce harm?
- Any additional tests?



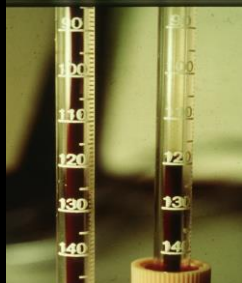
The Differential

- Cranial Arteritis
- Arteritic Ischemic Optic Neuropathy
- Temporal Arteritis
- Carotid Artery Disease
- Hypertensive Crisis
- Impending CVA



The Tests

- BP
- ESR
- CRP
- CBC
- **ESR >47**
- **CRP > 2.45**



Pain is NOT a disease-It is a sign of a disorder that must be diagnosed in conjunction with the management of the pain.

What is Pain?

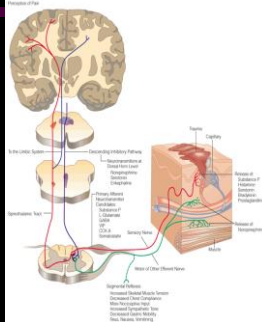
- Any unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- 75 million suffer from chronic pain
- 1/3- 1/2 require daily pain management

Analgesia VS Inflammation

- Choose the proper agent
- Choose the proper dose
- Dosage for the management of inflammation is higher than that for analgesia
- Side-effects increase with higher dosages

- Pain mechanisms are complex
- Peripheral VS Central Pain
- Direct nerve stimulation-Drop hammer on toe
- Inflammatory pain-Prostaglandins
- Tissue damage-Via infection or trauma

Why?? Why do I Have Pain?



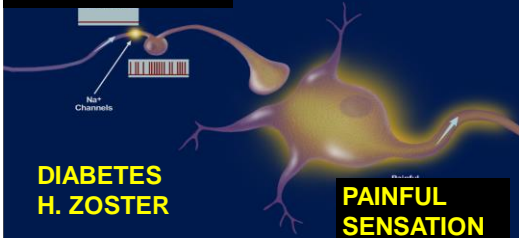
When? @ @ @ @ @

When Do I Need to Consider Pain Management?

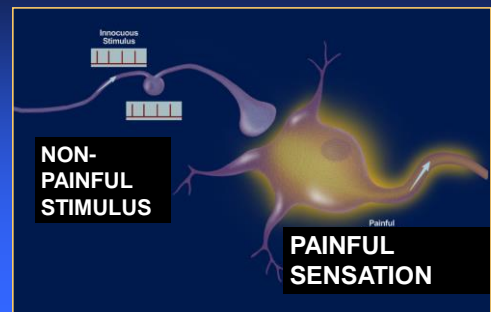
- Listen to your patient...IT HURTS!
- Be aware of clinical procedures and ocular disorders that are associated with significant

Neuropathic Pain: Primary neuropathic

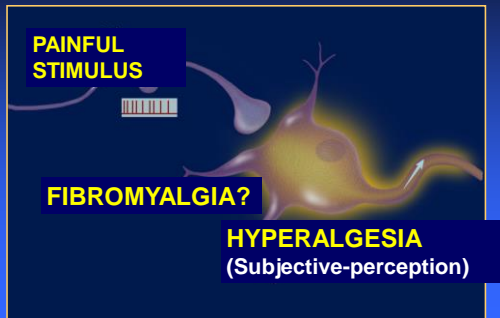
NO STIMULUS



Neuropathic pain: Allodynia



Neuropathic Pain: Hyperalgesia



Acute Pain

- ~ specific and obvious cause (e.g. trauma, surgery)-ALWAYS FIND CAUSE
- ~ limited duration
- Resolves when the source of pain is detected and treated
- ~ requires topical/local treatment
 - Fewer side effects/complications

Physiologic Effects of Pain

- Tachycardia
- Systemic hypertension
- Tachypnea
- Can exacerbate pre-existing cardiovascular disease

Psychological Effects of Pain

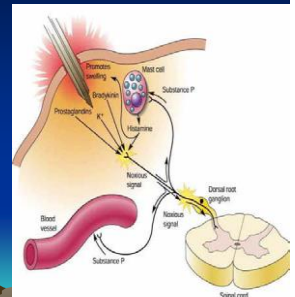
- Poor sleep patterns
- Anxiety
- Uncooperativeness

Analgesia

- The removal of pain
- Peripheral Agents: NSAID's
- Central Agents: Opiates
- Acetaminophen

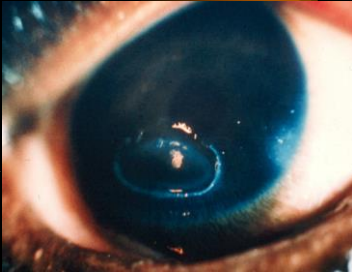
Pain Mediators

- Tissue injury causes release of chemicals
- They sensitize or activate receptors
- Neurons release *substance P*, which stimulates mast cells and blood vessels
- Histamine released from mast cells and bradykinin released from blood vessels add to pain stimulus



Indications

- Abrasions
- Lacerations
- Thermal and Chemical injury
- Dacryocystitis
- Bacterial corneal ulcers
- Cryo therapy
- Micropuncture



**Ester is NOT your Jewish aunt-
It's a new approach to disease
management**

- It's about time we had a better anesthetic than proparacaine



**Proparacaine-A good anesthetic for
the central cornea, but not much else.**

Problems:

Efficacy

No limbal or
conjunctival
coverage

Allergy



**Name the best AMIDE anesthetic for
LASIK, topical cataract surgery and
lacrimal procedures.**

- 1. Proparacaine
- 2. Tetracaine
- 3. Lidocaine ←
- 4. Cocaine
- 5. Benoxinate

- **THINK AMIDES, NOT ESTERS**

**YOU DON'T NEED A NEED
TO USE LIDOCAINE IN THE
EYE**



**Topical Lidocaine is a BETTER
anesthetic**

- **BENEFITS:**
- **NO CROSS SENSITIVITY**
- **EFFICACY ON VASCULAR TISSUE**
- **NO LOCAL METABOLISM**
- **LONGER LASTING**

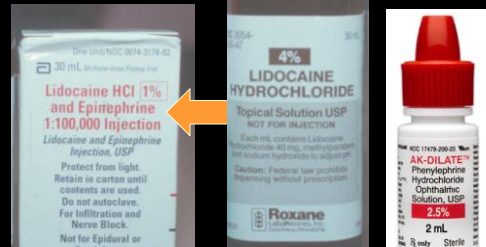


Available dosage forms

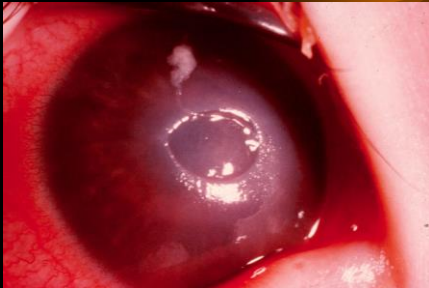
- 50cc bottle 4%-can be autoclaved
- 5cc 3.5% ophthalmic gel
- No preservatives

Want less bleeding and longer action-THINK SYNERGISM

$$1 (+) 1 = 3$$



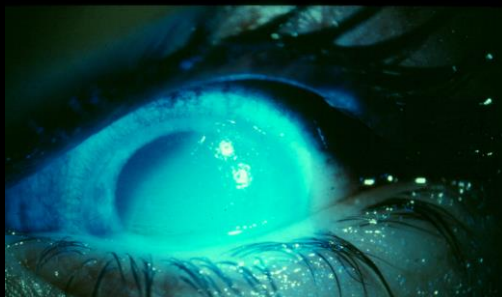
Anesthetics are NOT Harmless!!



Clinical Examples

FIRST, TX the primary condition, however, don't ignore pain management

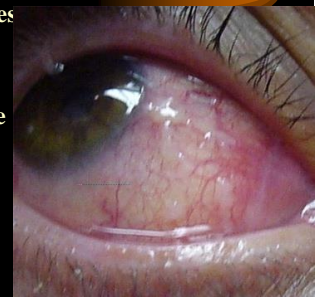
QUICK-MAKE A PROGNOSIS OR DOC-AM I GOING TO LOSE MY EYE?!!



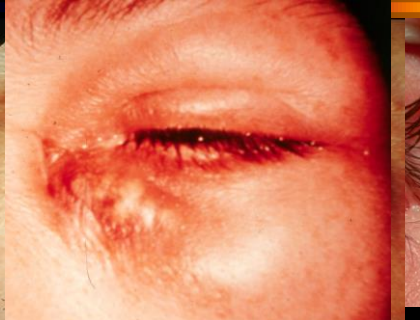
Caustic Chemical Burns

Same as thermal with:

- Balanced sterile rinses
- Monitor ocular pH
- Limit topical steroid to 1 week/collagenase activity
- PEARL: Think Vitamin C



Infection Hurts



Corneal Erosion



Erosion management

- PEARL: Think Doxycycline
- Watch out for smokers-Vitamin C

Watch Out for those Air Bags

- Blunt trauma to cornea produces a concussive trauma
- Abrasive surface can denude the epithelium completely
- Temporary to permanent stromal edema and hazing-decompensation due to endothelial shock
- Often an associated uveitis/hyphema and other forms of blunt ocular traumatic injuries



Analgesia VS Anti-inflammatory Therapy

- NSAID's are both analgesic and anti-inflammatory agents
- Anti-inflammatory dose is higher than analgesic dose
- Higher dosages = greater side-effects

Analgesic Pharmacology

- Tylenol/Acetaminophen/(N-Acetyl-P-aminophenol)/APAP
- Unknown central mechanism
- Anti-pyretic: Hypothalamus
- No anti-inflammatory effect @ @ @ @
- No inhibition of platelets @ @ @ @

Acetaminophen is a Safe Drug?

Drug of Choice (DOC) in:

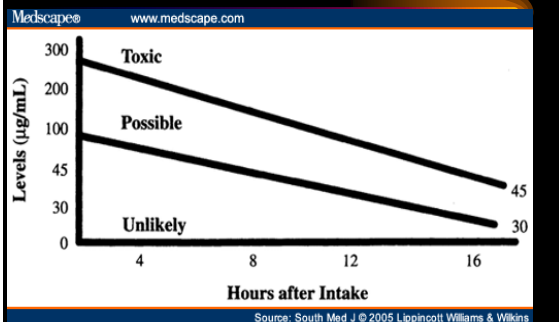
- Children
- Viral induced fever
- Pregnancy @@@@
- Nursing mothers
- No GI distress
- No Increase in Bleeding? @@@@



If They Like to Drink, Think Twice About Acetaminophen

- Acetaminophen associated with liver failure in alcoholics (>3 drinks/d)
- Liver failure = decreased drug metabolism = overdose
- Reduced vitamin K clotting factors = increased bleeding
- Max adult dose = 4gm/D = 8 extra-strength Tylenol per 24 hours (2.6gms?)
- 5% of metabolites hepatotoxic

Acetaminophen toxicity



Medicines for Fever or Pain Relief

Acetaminophen Dosing Chart

Acetaminophen (Tylenol) is available without a prescription. Determine the correct dosage by finding your child's weight in the top row of the table. You may repeat the dosage every 4 to 6 hours as needed. Do not give acetaminophen more than 5 times a day. Do not use acetaminophen in children under 3 months of age. If your infant has a fever during the first 12 weeks of life, see your child's health care provider.

Weight	7-13 lbs	14-20 lbs	21-27 lbs	28-41 lbs	42-55 lbs	56-83 lbs	84-111 lbs	112+ lbs
Miligram dosage	40 mg	60 mg	120 mg	160 mg	240 mg	325 mg	480 mg	650 mg
Infant drops 80 mg/0.5 ml 1 dropper=0.5 ml	0.4 ml	0.8 ml	1.2 ml	1.6 ml	2.4 ml			
Children's liquid 160 mg/5 ml (1 tsp)	1/2 tsp (1.25 ml)	1/2 tsp (2.5 ml)	3/4 tsp (3.75 ml)	1 tsp (5 ml)	1 1/2 tsp (7.5 ml)			
Chewable Tablets 80 mg each			1 1/2 tablets	2 tablets	3 tablets	4 tablets	6 tablets	8 tablets
Junior strength Tablets 150 mg each				1 tablet	1 1/2 tablet	2 tablets	3 tablets	4 tablets
Adult Strength Tablets 325 mg each						1 tablet	1 1/2 tablets	2 tablets

Abbreviations: mg = milligrams ml = milliliter tsp = teaspoon

Suppositories: Acetaminophen is also available as a rectal suppository in 120-mg, 325-mg, and 650-mg dosages. Suppositories are useful if a child with a fever is vomiting often or having seizures caused by the fever. Use the same dose as listed above for the suppository. Most suppositories can be cut (for example, cut in half) to supply the right dose for your child's age.

NSAID's: THE CYCLOOXYGENASE BLOCKERS

Salicylates

- Block cyclooxygenase
- Analgesic vs Antiinflammatory dose
- Acetylated vs non-acetylated

Acetylated VS Non-acetylated Salicylates

Non-acetylated developed to reduce:

- GI bleeding
- GI Upset

Acetylated: ASA: Aspirin

- Irreversible block of platelets
- Best for use as an anti-coagulant
- None are safe in potential bleeders



THE SECOND GENERATION NSAID's

- Less bleeding potential
- Less GI Upset
- Greater efficacy
- Greater potency
- All second generation drugs have the same efficacy in EQUIVALENT DOSAGES AND THE SAME SIDE-EFFECTS



EQUIVALENT DOSAGES

- 3200mg of ibuprofen = (800mg QID)
- 20mg of Feldene = (20mg/D)
- 750mg of Naprosyn per day (375mg BID)
- Only differ in 1/2 life = Dosing frequency
- Only differ in dosage = Potency

NSAID SIDE-EFFECTS

- Inhibit platelets: Only ASA is irreversible
- Allergic to one, allergic to all
- Avoid in asthmatics and those with nasal polyps-Increased incidence of allergy
- Watch out for protein binding in Type II diabetics@@@
- Renal insufficiency
- CHF

NSAID SIDE-EFFECTS

- Kids with fever: Avoid ASA
- Avoid pregnant or nursing mothers
- Those with GI problems
- Cytotec: An artificial prostaglandin would protect the stomach in LONG-TERM NSAID users-GREAT FOR CONSTIPATION

THE 3RD GENERATION NSAID'S THE PRO-DRUGS

- Nabumetone (Relafen): Fewer GI Side-effects
- Less problems with reduced renal function
- BID dosing

New NSAIDS

- New COX-2 inhibitors for acute pain
- Vioxx , hopefully not the patient, is dead
- Celebrex 200mg/D max dose
- Celebrex is a sulfonamide
- Look close-they will soon be gone
- Don't prescribe them



Ibuprofen-The Best of the NSAID's

- Cheap
- Flexible dosage Schedule

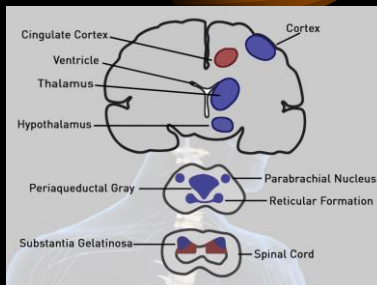


OOOHHH, That's GOT to Hurt!!



Opioid receptor types

- MU
- Kappa
- Delta



MU Opioid receptors

- **Classic morphine receptor**
- Located in brain and spinal cord
- Stimulated by endogenous endorphins
- Binding of drug to these receptors produces analgesia/sedation/decreased BP/itching/nausea/euphoria/decreased respiration/
- **Effects decline as drug tolerance develops**
- Narcotic antagonists block these receptors

Opiate Analgesics

- Block central pain receptors, reduce perception of pain-They feel pain, but don't care
- Allergic to one opiate, allergic to all opiates
- Know your schedules
- Schedule II, high abuse, V= low abuse
- **Know your side-effects/autonomics**

Side-effects

- **Respiration-sleep apnea/COPD**
- **Urinary tract/the big prostate/incontinence TX**
- **GI Tract: The food stops here**
- **Interaction with other anticholinergics/**
- **DRY/DROWSINESS/GLC**

COMBINATION OPIATE ANALGESICS

- Propoxyphene + ASA = Darvon empd
- Propoxyphene + APAP = Darvocet
- Codeine + Tylenol 1,2,3,4
- Hydrocodone + APAP = Vicodin
- Oxycodone + ASA = Percodan
- Oxycodone + APAP = Percocet

DEA MATH

- MO 0182597
- The sum of the 1ST, 3RD & 5TH:
 $0 + 8 + 5 = \underline{13}$
- The sum of the 2ND, 4TH & 6TH:
 $1 + 2 + 9 = \underline{12} \times 2 = \underline{24} + \underline{13} = \underline{37}$

PROPOXYPHENE = DARVON

- Relatively poor analgesia
- Lots of sedation
- Neurological side-effects
- Use if you want them to sleep a lot
- Darvocet N 50 and 100 are the best of group = propoxyphene napsylate with acetaminophen



Which Tylenol with Codeine Should You Use?

All contain 5 grains of APAP (325mg)
WITH:

- Tylenol #4 = 1 grain (60mg) codeine
- Tylenol #3 = 1/2 grain (30mg) codeine @ @ @ @
- Tylenol #2 = 1/4 grain (15mg) codeine
- Tylenol #1 = 1/8 grain 7.5mg codeine

A CLINICAL MOMENT

36 Y/O construction worker suffers an orbital blow-out fracture, complains about severe pain, requests pain reliever

Write him a prescription for acetaminophen with codeine-give him the maximum pain relieving dosage of the drug

John Doe 7/20/00
100 Low Life Ln.

Acetaminophen with Codeine #3

#20 (Twenty)

SIG: i-ii tabs q 4-6H prn pain

Refills: Zero

B. Onofrey MO 0182597

ALWAYS PRESCRIBE FROM THE BIG BOTTLE



IF YOU SAY 3 AND THEY SAY 4-
SHOW THEM THE DOOR

Oxycodone, The "BIG GUN"

- With ASA = Percodan
- With APAP = Percocet
- Schedule II drug = High abuse
- Better alternative with a schedule III drug?



That all fine and good butttt:



- @ @ @ @ @ @ @ @

Ibuprofen/acetaminophen

- Incredible synergism @ @ @ @ @ @
- Non-narcotic drugs
- Non RX drugs
- Inexpensive
- Monitor for sensitivity to either drug
- No motrin in pregnancy/with blood thinners/GI problems/renal disease/CHF

Ibuprofen/Acetaminophen Indication/dosage forms

- Indications:
- Mild to severe pain
- Dosage forms
- 400-600mg motrin with 500-1000mg acetaminophen (Do not exceed 4 gms acetaminophen/day)
- No acetaminophen for persons that regularly consume daily alcohol

HOW ABOUT ULTRAM?

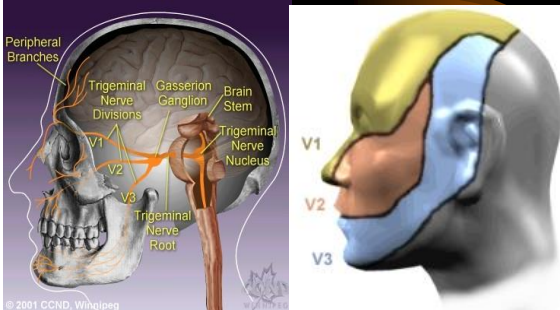
- A synthetic opiate with slightly reduced opiate side-effects
- NOT for opiate allergies
- Not for addicts-Induce withdrawal
- Has produced addiction
- 50-100mg QID prn-max 400mg/D
- >65, then 300mg/D max
- Ultracet, like Tylenol #3



A Potential Dis-zoster



Trigeminal N.-The 5th Cranial N



Who gets Post-herpetic Neuralgia

- Immunocompromised folk
- The elderly
- Best treatment is prophylactic TX

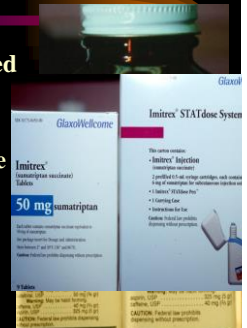
Neurontin: The New "Big Dog" for chronic pain

- Huge dosage range: 100-5000mg/d
- Must start slow
- Must give enough



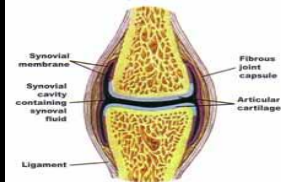
THE HEADACHE PILLS- NEVER USE THEM

- HA is a DX of exclusion
- Don't cover-up undiagnosed pain
- We must exclude other causes, but WE don't make the final DX
- Let PCP or neurologist manage pain AFTER final DX made



Rheumatoid disease

- A disease of inflammation and autoimmunity
- Affects joints-localized to the synovial membrane



Cause of RA

- **Genetic predisposition: Rheumatoid factor**

An IgM antibody (auto-immune) against IgG

Present in most RA patients

Produced by B-cells (humoral anti-body) in synovial fluid

Progression

- RF factor/IgG complex triggers complement = tissue damage
- Damage attracts cellular response- PMN's and macrophages
- Pannus formation in joint : PMN's (+) macrophages (+) fibroblasts form scar tissue in joint
- IL-1 and TNF alpha produced by pannus stimulate osteoclasts from macrophages and produce bone reabsorption = joint damage

NSAID's and RA

- Reduce pain in RA
- NSAID'S DO NOT prevent joint destruction in RA!!

Meet the DMARD's

- **D** – Disease
- **M** – Modifying
- **A** – Anti-
- **R** – Rheumatic
- **D** - Drugs

Indications

- Relieve or reduce pain
- Improve function
- Reduce joint inflammation (swelling, tenderness & reduced ROM)
- Prevent joint damage and deformity
- Prevent disability
- Improve quality of life
- More toxic than NSAIDS

Categories of DMARD's

- **FIRST GENERATION**

Gold compounds: aurothioglucose

Action: Inhibit macrophage migration and phagocytosis

Toxic: Colitis and reduced immunity

Required weekly IM injections

Categories of DMARD's

- **ORALS: 2nd generation**

Hydroxychloroquine Cyclophosphamide

Leflunomide Cyclosporine

Methotrexate Minocycline

Sulfasalazine Penicillamine

Azathioprine

Methotrexate and leflunamide

- Cytotoxic B/T cell inhibitors
- Block pyrimidines (Inhibits DNA synthesis)
- **Prevent B and T cell proliferation and therefore prevent formation of RF**

Hydroxychloroquine/Plaquenil

- Inhibits lymphocytes and IL-1 production
- Dose : 200-400mg/D
- Monitor for maculopathy
- Occurs rarely/increased risk after cumulative dose of 700gm (>5yrs TX)

Categories of DMARD's

- **BIOLOGICALS (Injectables)**
- **3rd generation TNF alpha antagonists**

Abatacept : Orencia

Adalimumab : Humira

Anakinra : (Kineret)

Infliximab : Remicade

Rituximab : Rituxan

Biologicals

- Prevent bone absorption and joint deformation
- Protein compds-must be injected
- Cost: \$10K/yr
- **Adverse effects:**
Liver toxic
Opportunistic infections
Death

RA TX

OLD WAY

- Tx conservatively
- With NSAIDS- DMARDS only if severe

NEW WAY

- TX aggressively with DMARDS ASAP- "window of opportunity is early in TX"
- Combination TX is common

QUESTIONS?

INFLAMMATION-THE GOOD

The bodies normal physiologic response to tissue damage

- Destroys invading organism
- Scavenge dead tissue
- Begin repair process: Scarring



INFLAMMATION: THE BAD

If inflammation is the major mechanism of local damage, then it must be controlled. This control must within the context of the primary cause of the inflammation.

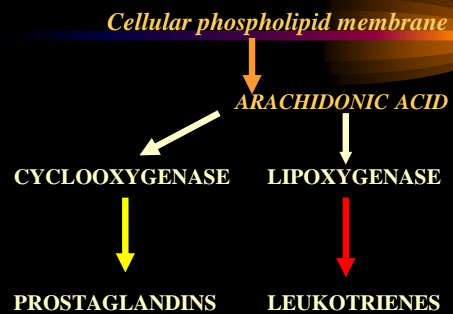
- Trauma
- Infection
- High IOP
- Immune disorder

THE CARDINAL SIGNS OF INFLAMMATION

- Rubor: Redness
- Calor: Heat
- Dolor: Pain
- Tumor: Swelling

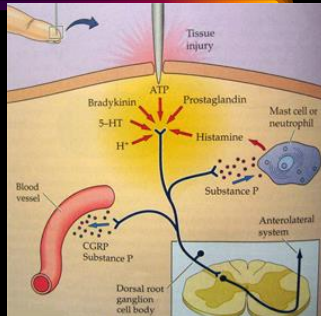


THE INFLAMMATORY CASCADE



Chemical stimulation of nociceptors

- Prostaglandins
- Bradykinin
- Potassium
- Serotonin
- Histamine



Steroids and RA

- Block production of IL-1
- Dramatic, rapid suppression of inflammation
- Short term, intermittent use only –due to SE's
- Used until DMARDS take effect
- Local joint injections can produce degeneration of cartilage

Scleritis is Serious Inflammation STEROID VS NSAID



NSAIDS OF COURSE THEY'RE SAFER?

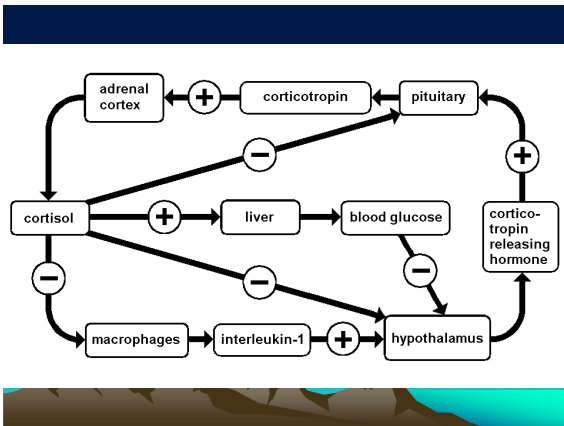
- Only anti-inflammatory in high doses
- Think RK good for -11.00 myope or LASIK
- GI ulceration
- Renal failure
- Congestive heart failure
- Type II diabetes
- POOR anti-inflammatory effect

Steroids Are Safer? You must be kidding

- Extremely effective anti-inflammatory effect
- Safe for short term use if.....
- No GI ulcer
- No psychotic
- No high BP
- No diabetes

THE NEGATIVE FEED BACK LOOP

- Hypothalamus: CRF: Corticotropin releasing factor
- Anterior pituitary: ACTH: Adrenocorticotrophic hormone
- Adrenal gland: Cortisol: Glucocorticoid
- Adrenal gland: Aldosterone: Mineralocorticoid effect for H₂O/Na⁺ balance
- Artificial steroids inhibit CRF



- ## STEROID INDICATIONS
- Intractable uveitis
 - Herpes zoster
 - Acute anaphylaxis
 - Temporal arteritis@@@@@
 - Scleritis

- ## STEROID PRODUCTS SYSTEMIC
- Know steroid equivalents
 - Medrol dospak
 - Prednisone-very flexible dosage
 - Methyl prednisolone for IV injection-solu-medrol
 - Kenalog for local repository effect good for chalazia
- 

- ## STEROID EQUIVALENT DOSAGES
- Prednisone: 5mg@@@
 - Methylprednisolone: 4mg@@@
 - Hydrocortisone: 25gm
 - Dexamethasone: 0.75mg
 - Cortisone

- ## STEROID DOSAGES: In prednisone equivalents
- Temporal arteritis: 80-100mg/d
 - Uveitis: 40-60mg/d
 - Acute allergy: 20-40mg/d
 - Children: 1mg/kg/d
 - Rapid taper = 50% decrease q 3d
 - ADT = dbl dose QOD, not necessary for less than 2 weeks TX@@@@
 - Medrol dospak is the best

The Ultimate Oral Steroid



Roxy®
Methylprednisolone Tablets, USP
4 mg
21-Pack

Each tablet contains Methylprednisolone, USP, 4 mg.

Directions for oral-use package insert.

CAUTION: Federal law prohibits dispensing without prescription.

Store as directed from manufacturer, USP REF-1 (2014-01-01).

MANUFACTURED BY: ROYAL PHARMACEUTICALS, INC., ROCKVILLE, MD, USA.

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100 mg
80 mg
60 mg
40 mg
20 mg

Medrol Dose-pak Indications/dosage forms

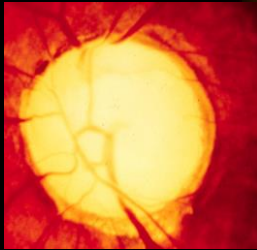
- Indications:
- Anterior uveitis/scleritis/Type I allergy
- Dosage form:
- Pre-labeled with descending dosage (automatic daily taper over 6 days of TX)
- Always take with food/avoid in diabetics/GI bleeders/blood thinners/NSAIDS/hypertension/psychosis

STEROID SIDE-EFFECTS

- Inhibit good immune response
- Exacerbate infection
- Sodium and water retention
- Increase BP
- Exacerbate diabetes mellitus @@@
- Steroid cataract and glaucoma @@@
- Psychosis @@@
- Addison's and Cushing's disease



Topical Steroids are NOT Harmless



Thank You