NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- MRS. M.M. HAS A 3 YR. HX OF PROGRESSIVE RIGHT HIP PAIN.
- THE PAIN INCREASES WITH WEIGHT BEARING ACTIVITY.
- PT. HAS BEEN ON ACETAMINOPHEN WITHOUT RELIEF.
- PERTINENT LABS INCLUDE CREATININE OF 1.4,
- X-RAY OSTEOARTHRITIS HIP.
- YOU PRESCRIBE A NONSTEROIDAL ANTI-INFLAMMATORY DRUG.

- WHAT ARE THE PRIMARY MECHANISM OF ACTION OF NSAIDS.
- WHAT EFFECT DO THEY HAVE ON COX-2 PRODUCTION.
- WHAT SIDE EFFECTS ARE SEEN WITH NSAIDS.
- WHAT GROUP OF PATIENTS ARE AT RISK FOR TOXICITY FROM NSAIDS?
- HOW DO YOU MONITOR PTS. ON NSAIDS?
- WHAT ARE THE POTENTIAL ADVANTAGES AND DISADVANTAGES OF COX-2 INHIBITORS

ROLE OF PROSTAGLANDINS

PATHOLOGIC	PHYSIOLOGIC
FEVER	TEMPERATURE CONTROL
ASTHMA	BRONCHIAL TONE
ULCERS	CYTOPROTECTION
DIARRHEA	INTESTINAL MOBILITY
DYSMENORRHEA	MYOMETRIAL TONE
-	SEMEN VIABILITY
INFLAMMATION	
BONE EROSION	
PAIN	

FUNCTION OF PROSTAGLANDINS IN INFLAMMATION

- PGE_2, PGI_2
  VASODILATION,
  ACT SYNERGISTICALLY WITH OTHER MEDIATORS
  HISTAMINE, COMPLEMENT, LTB_4
  BRONCHODILATATION
  INHIBITION OF PLATELET AGGREGATION
- TXA_2
  PROMOTION OF PLATLET AGGREGATION

FUNCTIONS OF COX

COX-1	COX-2
CONSITUTIVELY EXPRESSED	INDUCIBLE
HOUSEKEEPING FUNCTIONS	
PRESENT IN EVERY ORGAN STOMACH, INTESTINE, KIDNEY PLATLETS, VASCULAR ENDOTHELIUM	INFLAMMATORY AND NEOPLATIC SITES ALSO PRESENT IN KIDNEY, UTERUS. OVARY BRAIN, SMALL INTESTINE

NSAIDS-THERAPEUTIC EFFECTS

- ANALGESIA
- ANTI-INFLAMMATORY
- ANTI-PYRETIC
- ANTI-NEOPLASTIC

EFFECTS OF NSAIDS

- INHIBITION OF
  - CYCLOOXYGENASE ENZYMES
  - LIPOXYGENASE ENZYMES
  - SUPEROXIDE GENERATION
  - LYSOSOMAL ENZYME RELEASE
  - NEUTROPHIL ACTIVITY
  - LYMPHOCYTE FUNCTION
  - CYTOKINE RELEASE
  - CARTILAGE METABOLISM

COX-1: *Constitutive*

- Homeostatic
  - Protection of gastric mucosa
  - Platelet activation
  - Renal functions
  - Macrophage differentiation

COX-2: *Regulated*

- Pathologic
  - Inflammation
  - Pain
  - Fever
  - Dysregulated proliferation
- Tissue Repair
- Physiologic
  - Reproduction
  - Renal functions
  - Other (see text)
- Development
  - Kidney

- Similar to non-specific COX inhibitors
  - Anti-inflammatory
  - Analgesic
  - Anti-pyretic
  - Some renal effects, e.g. sodium excretion, blood pressure

- Different from non-specific COX-inhibitors
  - No anti-platelet effects
  - Reduced endoscopic GI erosion and ulceration
  - Some renal effects, e.g. possibly less alteration of RBF and GFR

NSAIDS: PHARMACOLOGY

- GOOD ABSORPTION
- HEPATIC METABOLISM
- HIGHLY PROTEIN BOUND
- BOTH ENTEROHEPATIC AND RENAL EXCRETION
- VARIABLE HALF LIFES

HALF-LIFE NSAID

SHORT HALF LIFE- MORE RAPID EFFECT AND CLEARANCE

- IBUPROFEN,DICLOFENAC,INDOMETHACIN,

LONGER HALF LIFE- SLOWER ONSET AND SLOWER CLEARANCE

- NAPROSYN, CELOCOXIB, ROFECOXIB
- NABUMETONE, PIROXICAM

DRUG INTERACTIONS

- ANTI-HYPERTENSIVE RX
- PHENYTOIN
- ANTI-COAGULANTS
- METHOTREXATE

NSAIDs TOXICITY

- GASTROINTESTINAL
- RENAL
- HEMATOLOGIC
- CNS
- HEPATIC
- SKIN
- ALLERGIC

NSAIDS- GI TOXICITY

- **SYMPTOMS: FREQUENT**
- **POOR CORRELATION WITH ENDOSCOPY**
- **EROSIONS, ULCERATIONS, BLEEDING**
- **COLITIS**
- **RX:PROTON PUMP INHIBITORS**
  - **HIGH DOSE H2 BLOCKERS**
  - **SUCRAFATE**
  - **MISOPROSTOL**
  - **COX-2 INHIBITORS**
  - **DISCONTINUTATION**

NSAID GI TOXICITY

ENDOSCOPIC ULCERS

- GASTRIC 15-30%
- DUODENAL 10%

COMPLICATIONS

- PERFORATIONS, BLEEDING
- COST ESTIMATES- $4 BILLION
- MORTALITY 7500 PER YEAR
- OVERALL RISK 1/1000

RISK FACTORS FOR NSAID GI TOXICITY

- OLDER AGE
- STEROIDS
- RA
- HX OF PUD
- HIGHER DOSE NSAID

NSAIDs GI TOXICITY

- AVOIDANCE OF NSAIDs
- TREATMENT WITH
  - H2 BLOCKERS AT HIGH DOSES
  - PROTON PUMP INHIBITORS
  - MISOPROSTOL
  - SUCRAFATE
- COX-2 SPECIFIC NSAIDs

COX-2 TOXICITY:GI

- SYMPTOMS SIMILAR TO NONSELECTIVE NSAIDS
- ULCERATIONS MUCH LESS THAN NONSELECTIVE
- RISK OF BLEEDING AND PERFORATIONS LESS
- EFFECTS ON COLONIC POLYPS AND CANCER

NSAIDS- HEMOSTASIS

- IMPAIRED PLATELET AGGREGATION
- PROLONGED BLEEDING TIME
- ANTI-COAGULATION RX
- COX-2 INHIBITORS

NSAIDS: CNS TOXICITY

- HEADACHE
- CONFUSION
- DIZZINESS
- MOOD ALTERATION, DEPRESSION
- ASEPTIC MENINGITIS

COX-2: CNS

- COX-2 PREDOMINANT ISOFORM IN NEOCORTEX, HIPPOCAMPUS
- STUDIES IN ALZHEIMER'S IN PROGRESS

NSAIDS- LIVER

- TRANSAMINITIS
- HEPATITIS

NSAIDS: RENAL

- DECREASED RBF: DECREASED RENAL PG
- RISK FACTORS: VOLUME DEPLETION
  RENAL, LIVER DISEASE
  VASCULAR DISEASE
- EDEMA, HBP, INCREASED CREATININE
- NEPHROTIC SYNDROME: INTERSTITIAL NEPHRITIS
- ELECTROLYTE IMBALANCE: K+
- ATTENUATION OF BP MEDS
- PAPILLARY NECROSIS
- STONES

COX-2: RENAL

- KNOCK OUT MODELS- RENAL DISEASE
  - PATHOLOGY- FIBROSIS,INFLAMMATION,PAPILLARY CHANGES
- CLINICAL STUDIES

  EDEMA- RESOLVES WITH DRUG WITHDRAWAL.

NSAIDS: HYPERSENSITIVITY

- URTICARIA
- ANAPHALAXIS
- BRONCHOSPASM
- NASAL POLYPS, ASTHMA

COX-2: Reproductive

- KNOCK OUT MODELS- INFERTILITY
- COX-2 INDUCED BY LH PRIOR TO OVULATION
- COX-2 INDUCED AT DELIVERY
  - INHIBITORS MIGHT BE OF VALUE IN PREVENTING PRETERM DELIVERY

COX-2: Hematology

- NO EFFECT ON WBC OR HB
- NO EFFECT ON PLATELET AGGREGATION
  - PLATELETS EXPRESS ONLY COX-1
  - NEED TO USE LOW DOSE ASA FOR CARDIAC
  - CAN BE USED WITH COUMADIN BUT COUMADIN DOSE MAY NEED ADJUSTMENT

NSAIDS: CANCER

- DECREASE IN COLON CANCER
- DECREASE NUMBER AND SIZE OF ADENOMAS IN PTS WITH HX OF FAMILIAL ADENOMAS
- COX-2 INHIBITORS APPROVED IN FAMILIAL POLYPOSIS

NSAIDS:CANCER PREVENTION

- INDUCTION OF COX-2 IN RODENT AND HUMAN COLORECTAL ADENOMAS AND CARCINOMAS
- COX-2 INHBITION- REGRESSION OF NEOPLASTIC POLYPS AND PREVENTION OF THEIR DEVELOPMENT
- ROLE OF COX-2 INHIBITORS IN CANCER PREVENTION IN PROGRESS

COX – 2 INHBITIORS

- CELECOXIB AND ROFECOXIB
- SIMILAR IN EFFICACY TO NON SELECTIVE NSAIDS
- APPROVED IN OA, RA, PAIN, FAMILIAL POLYPOSIS
- LESS GASTRIC ULCERATIONS, GI SYMPTOMS STILL OCCUR BUT LESS
- LESS SERIOUS GI EVENTS- PERFORATIONS, BLEEDS THAN NONSELECTIVE THERAPIES
- OTHER TOXICITIES SIMILAR
- NO EFFECT ON PLATELET FUNCTION- MUST USE ASA IN CARDIAC PTS

NSAIDS: WHAT PATIENTS WANT TO KNOW

- GI INTOLERANCE
- GI ULCERATION, BLEEDING
- EDEMA, HBP
- CNS
- RASH
- LIVER