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MSS

Musculoskeletal System

Pharmacology

Doctor 2018 | Medicine | JU

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Notice: This sheet is written according to section 3

❖ Continuation of Nonsteroidal Anti-inflammatory drugs (NSAIDs)

ASPIRIN

- Aspirin is the prototype of NSAIDs
- Aspirin works by inhibiting the cyclooxygenase enzyme, it inhibits both isoforms of cyclooxygenase: **COX-1 and COX-2**
- It is a weak organic acid and **irreversible inhibitor** of these enzymes (COX-1 and COX-2). (All other NSAIDs are **reversible**)
- It is one of the oldest drugs that were synthesized, it was used early in the 1900s, but was synthesized in 1883.
- It was officially approved for use by the FDA in 1939.

MOA FOR ASPIRIN

- Aspirin is the synthetic form of **salicylic acid.**
- ➢ In the body, aspirin gets hydrolyzed or converted by esterases into salicylic acid, which has **anti-inflammatory, antipyretic, and analgesic effects.**
- ➢ The effects of salicylic acid is mediated through **inhibition of the production of prostaglandins.**
- ➢ The antipyretic effect happens because we inhibit the production of prostaglandins in the *CNS*, in the thermoregulatory center in the hypothalamus, while the anti-inflammatory effects due to inhibition of prostaglandins synthesis at *peripheral sites*.
- ➢ Additionally, Aspirin is an **analgesic agent,** so it decreases prostaglandin synthesis preventing the sensitization of pain receptors at both mechanical and chemical stimuli
- ➢ Aspirin can have some **CNS effect** on the inhibition of the pain by decreasing pain stimuli at the subcortical spaces/sites.

QUESTION: WHAT IS THE MAJOR SIDE EFFECT THAT MIGHT OCURR DUE TO THE USE OF NSAIDs? **GI irritation.**

Even though, aspirin is associated with this side effect (GI irritation) for the patient, aspirin is still one of the most commonly prescribed used drugs for the treatment of anti-inflammatory disorders

ASPIRIN (SALICYLATE)

- **Most commonly used anti-inflammatory agents**
- **15%** of patients show intolerance or are allergic to aspirin. In these patients, we substitute the use of aspirin with other anti-inflammatory agents.
- Aspirin is unique in the ability to acetylates the cyclooxygenase **irreversibly.** All other NSAIDs are **reversible inhibitors of cyclooxygenase.**

ASPIRIN ANTI-INFLAMMATORY EFFECT

- This effect is a result of its ability to **diminish the formation of prostaglandins that mediate the inflammation process.**
    - Aspirin is the first line therapy for **rheumatoid arthritis.**
    - While aspirin inhibits the inflammatory and pain process associated with inflammatory diseases, such as **rheumatism,** but it does not slow the progression of the disease nor induce remission. It does not treat the cause of the disease rather it treats the sign and symptoms of inflammation that are bothersome to the patient.

ANTIPYRETIC ACTION OF ASPRIN

- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated.
- Impeding PGE2 synthesis and release resets the hypothalamus toward normal
- It rapidly lowers the the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating.
- Aspirin has no effect on normal body temperature
- **THIS ANTIPYRETIC EFFECT REFERS TO ALL NSAIDs.**

Aspirin has some adverse effects/toxicities related to inhibiting prostaglandins synthesis in other tissues :

RESPIRATORY ACTION OF ASPIRIN

- In therapeutic doses, it can **uncouple oxidative phosphorylation,** which leads to: elevated CO2 levels and increased respiration
- At higher doses, it effects directly in on the **respiratory center in the medulla,** resulting in: hyperventilation and respiratory alkalosis
- At toxic levels, the patient will have **paralysis in the respiratory muscles,** which will result in **acidosis.**

- BE CAREFUL ABOUT USES OF THIS DRUG AT THERAPEUTIC DOSES AND NOT TO REACH TOXIC LEVELS

GASTROINTESTINAL EFFECT OF ASPIRIN

- Aspirin prevents the prostaglandin synthesis in the stomach.
- **PGE2** (prostaglandin E2) synthesis in the stomach has a protective role by inducing a protective mucous layer in both the **stomach and small intestine**
- So in the presence of aspirin, prostaglandins are not formed, this loss of prostaglandins results in **increased gastric acid secretion and diminished mucus protection, that's why we have the side effect of GI irritation and/or increased susceptibility to a peptic ulcer.**

QUESTION: NOW WHAT IS THE SOLUTION TO THIS PROBLEM? (GI irritation + peptic ulcer) **we should give the patient drugs that treat peptic ulcer which include: proton pump inhibitors (PPIs), which are esomeprazole, lansoprazole, omeprazole**

QUESTION: WHAT IS THE ROLE OF PROSTAGLANDIN SYNTHESIS IN THE GI TRACT? **Prostaglandin synthesis in the stomach has a protective role by inducing mucous protective layer in both the stomach and small intestines**

ASPIRIN EFFECTS ON PLATELETS

- All of the NSAIDs inhibit COX-1 and COX-2, and by this inhibition through aspirin, there will be an inhibition of **thromboxane.**
- **THROMBOXANE**: has a role in inducing platelet aggregation.
- So at low doses (81 mg daily) of aspirin, we can **irreversibly inhibit the thromboxane (TXA2) production in platelets, through inhibiting COX-1 and COX-2 in the platelets thus decreasing platelet aggregation.**
- This is used as an prophylactic effect for preventing the occurrence of **thromboembolism in susceptible patients,** who have more tendency for these thromboembolic accidents.
- Because aspirin is an irreversible inhibitor and platelets are not true cells, meaning they do not have nuclei. So when we have this irreversible inhibitory effect, we have to synthesize more of the enzyme to regenerate the action of that enzyme, because platelets are not true cells, they are not going to be able to synthesize the enzyme, so the action of aspirin on the platelet will stay in the whole life cycle of the platelet

which is between **7-10 days.** As a result: there will be an increase of bleeding time when using aspirin.

- So we have to take this into consideration, when a patient wants to get a surgery and he's taking aspirin, you have to know there will be a chance of increased bleeding because of taking aspirin prophylactically for other diseases.

  NOTE: This characteristic of anti-platelet is shared by all NSAIDs, but because aspirin is able to give up this property, this particular concentration, which is 81mg, because it has the irreversible capability to inhibit the enzyme, it is used prophylactically for that condition while other NSAIDs they are not , even through they inhibit thromboxane synthesis, they will have an increased chance of thrombosis at higher doses they are utilized.

ACTIONS OF ASPIRIN ON THE KIDNEY

- Remember that NSAIDs are **nephrotoxic**
- Prostaglandins can cause **vasodilation of the blood vessels, the afferent blood vessels which go into the kidney.** Now when we have inhibition of prostaglandins there will be a decrease in the vasodilation, instead there will be vasoconstriction.
- In addition, decreased synthesis of prostaglandins may result in **retention of sodium and water** and may cause **edema** and **hyperkalemia** in some patients.
- EXCEPTION: **Interstitial nephritis (direct effect of toxicity on the nephron)** can occur with all NSAIDs, except for aspirin it does not have this effect.

THERAPEUTIC USES OF ASPIRIN

ANTI-INFLAMMATORY, ANTIPYRETIC, AND ANALGESIC USES

- Aspirin is **anti-inflammatory, antipyretic, and analgesic**
- Indication of aspirin is in the use for the **treatment of gout,** which is an inflammatory disease. Also used in the treatment of **rheumatic fever, osteoarthritis, and rheumatoid arthritis.**
- Commonly used in condition to relieve pain (analgesic effect), which include **headache, arthralgia, and myalgia.**

EXTERNAL APPLICATIONS

- Salicylic acid is used topically to treat corns and warts.
- Its action is de-keratinization or desquamation of the keratinized layer of the skin.

CARDIOVASCULAR APPLICATIONS

- Aspirin is used to **inhibit platelet aggregation.**
- Low doses of aspirin are used **prophylactically to:**
- Reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death
- Reduce the risk of death in those having an acute myocardial infection, angina, and other diseases associated with thrombosis in the body.

PHARMACOKINETICS – ASPIRIN

ADMINISTRATION AND DISTRIBUTION

- After administration of aspirin, it gets absorbed in the un-ionized form from the **stomach** and the **small intestine**. Now after absorption, protein binding takes place, most of the NSAIDs, including aspirin are extensively bound to plasma protein.
- **Rectal** absorption of the salicylate is **slow** and unreliable, but it's a useful route for administration to **vomiting children.**

DOSAGE

- Aspirin exhibit analgesic activity at **low** doses
- **Higher** doses of aspirin show anti-inflammatory activity.
- **Two 325-mg** aspirin tablets administered **four times** daily produce analgesia, whereas **higher dose** produce both analgesic and anti-inflammatory activity.
- For long term myocardial infarction prophylaxis, the dose is **81-162 mg/day**
- Those with RA or osteoarthritis, the initial dose is **3 grams/day**
- For stroke prophylaxis, the dose is **50 to 325 mg/day**

REYE'S SYNDROME

- Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing hypoglycemia.
- Features of Reye's syndrome: rash, vomiting, and liver damage
- One special thing about aspirin, it's associated with a condition called **Reye's syndrome**
- Children or teenagers below the age of 15 years old, if they take aspirin to treat pain or fever while they have a viral infection, for example: chicken pox or influenza. They then have a **higher risk** of getting Reye's syndrome.

- It can occur without the use of aspirin, but at a lower risk.

QUESTION : What is Reye's syndrome? **Dysfunction mainly in the liver or brain, reason for this is not known but it can happen with the use of aspirin with a viral infection, we then have more of a chance in developing this syndrome. It can occur with the absence of aspirin, regardless you should be cautious. The drug of choice to give in this situation is: acetaminophen or paracetamol**

DRUG INTERACTIONS:

- Salicylate is **90-95%** protein bound and can be *displaced* from its protein-binding sites, resulting in **increased concentration of free salicylate.**
- Aspirin could displace other highly protein-bound drugs, such as **warfarin, phenytoin or valproic acid,** resulting in higher free concentrations of the other agent.

NOTE: When there is an increased concentration of the free form of the drug, the effect of the drug will be increased, in addition there will be an increase in the toxic and therapeutic effect of the drug.

- We can not use aspirin with other NSAIDs, for example **ketorolac,** because then there will an increased risk of GI bleeding and platelet aggregation inhibition.

QUESTION: WHAT IS THE USE OF ASPIRIN IN PREGNANCY? **In general, aspirin is categorized as pregnancy category C EXCEPT in the third trimester, where it is classified as category D.**

QUESTION: WHAT DO THESE PREGNANCY CATEGORIES REFER TO? **The FDA classifies drugs according to the risk they might have. In pregnancy, there are different categories: A, B, C, D, and X. Category A means this drug is safe. Acetaminophen and Paracetamol is considered to be in category A. Category B is safe to give to pregnant females. Animals studies show that there are no risk on the upcoming fetus or Animals studies did show risk but history from the human use showed that there is no risk. Category C, here you have to put your judgement into use. In category C, animal studies did show risk, so CAUTION IS ADVISED. While we do not have enough data about the risk in humans, so it's the duty of the doctor to decide whether the *benefit outweighs the risk*, for example: the patient may have an infection and this patient will need an antibiotic for that infection, and this antibiotic**

FDA Pregnancy Categories

Category	Description
A	Controlled studies of pregnant women show no risk in first trimester
B	Animal studies show no risk, or animals show risk unconfirmed in humans
C	Animal studies show risk, caution is advised, benefits may outweigh risks
D	Evidence of risk to human fetus, benefits may outweigh risks in serious conditions
X	Risk outweighs benefit

Adapted from Dwosh E, et al. *Int MSJ*. 2003;10:52-59.

MedscapeCME

that's proper to be used is category C. So this infection may have a dangerous impact in the mother's life, so you have to give this antibiotic to the pregnant woman, even though their may be an effect on the fetus but we want to save the mothers life, so in result it's the doctors judgement in deciding whether the pregnant woman should take the drug that is in category C. Category D, there is evidence for risk in fetus, in certain serious conditions *sometimes* the benefit outweighs the risk, again here it's up to the doctor to decide. Category X, risk outweighs the benefit. Drug in category X are known to be *teratogenic,* for example: isotretinoin.

EXTRA RELATING TO EMBRYOLOGY (The doctor mentioned we will take this in embryology): Now we know that aspirin is category C in the 1st and 2nd trimester, but why? Remember we said that prostaglandins are vasodilators, so they are important for the integrity of the vasculature of the upcoming fetus. Now, why are they category D in the third trimester? A structure associated with fetal circulation called **ductus arteriosus** (it is a blood vessel in the developing fetus connecting the trunk of the pulmonary artery to the proximal descending aorta. It allows most of the blood from the right ventricle to bypass the fetus's fluid-filled nom-functioning lungs.) The fetus can not breathe air because the lungs are not completely developed, so they will not have the ability to respirate oxygen, meaning they will not need the function of the pulmonary artery that will go from the heart to the lungs to carry oxygen and return it back to the heart, because of this in the life of the embryo, there is a channel/small duct in between the pulmonary artery and aorta creating a shunt, meaning it avoids going to the pulmonary circulation. So this shunt takes the blood from the ventricle back to the aorta so it can get distributed in the body. Now after birth, this **ductus arteriosus** is closed immediately. Now what happens if we take aspirin or other NSAIDs in the last trimester, because there is a decrease in prostaglandins because of this decrease it will close the ductus arteriosus in utero resulting in **miscarriage (death of fetus).** That's why aspirin is categorized as category D during the 3rd trimester.

+ (condition related to embryology) **Patent ductus arteriosus:** is a medical condition in which the ductus arteriosus fails to close after birth. To fix this problem, we give NSAIDs, for example **indomethacin or ibuprofen,** which will stimulate closure of ductus arteriosus after birth.

TOXICITY

- Toxicity or overdose of aspirin is called **salicylism.**

- It is has the same and signs and symptoms that occur in people who have allergy or intolerance for aspirin. So what happens is: **nausea, vomiting, hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears)**
- Ingestion of as little as **10g of aspirin** can cause death in *children.*

QUESTION: WHAT HAPPENS IF WE HAVE TOXICITY OR SALICYLISM? **We have to take certain measures for example: IV administration of fluid, dialysis correction of acid-base and electrolyte balances.**

PROPIONIC ACID DERIVATIVES

- They include: **ibuprofen, naproxen, fenoprofe, ketoprofen, flurbiprofen**
- All of these drugs possess **anti-inflammatory, analgesic, and antipyretic activity.**
- Their **GI** effects are generally *less intense* than those of aspirin, although they have the GI irritation side effect
- These drugs are **reversible** inhibitors of cyclooxygenases
- They are bound to plasma proteins, so they are well absorbed after oral administration and are almost totally bound to serum **albumin.**
- They undergo **hepatic** metabolism and are excreted by the **kidney**
- The most common adverse effect are: **GI, ranging from dyspepsia to bleeding.**
- Also they have side effects involved in the **CNS, such as headache, tinnitus, and dizziness.**

Naproxen and Ibuprofen (propionic acid derivatives)

- Pregnancy: category C (1st and 2nd trimester), category D (3rd trimester)
- Increase the risk of cardiovascular thrombotic event (due to COX-2 inhibition mainly), MI and stroke
- Increase risk of GI bleeding
- Do not exceed ibuprofen 3200mg/day, and take with food or with water to avoid GI effect.

ACETIC ACID DERIVATIVES

- They include: **indomethacin, sulindac, and etodolac**
- Their anti-inflammatory properties are high, so they are used to treat many inflammatory conditions such as, **rheumatism, gouty arthritis, spondylitis.** But

the problem is they have higher toxicity than other NSAIDs, because of that higher toxicity, chronic use of these agents in high doses can be problematic which we will limit the use of these agents

- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis
- The adverse reactions caused by **sulindac** are similar to, but less severe than, those of the other NSAIDs, including indomethacin
- **Etdolac** has effects similar to those of the other NSAIDs

Indomethacin

- it's a **nonselective COX inhibitor,** in addition it has an effect on **inhibiting phospholipase A and C**, also can **reduce neutrophil migration**, and **decrease T and B cell proliferation**
- Can be used in: **juvenile rheumatoid arthritis, gout and ankylosing spondylitis**
- It has been used to **treat patent ductus arteriosus.**
- We have an **ophthalmic use** of this agent because it has power/superior ability as an anti-inflammatory used to inhibit inflammation, which this inflammation can happen after certain ophthalmic surgeries or procedures.
- There is an oral rinse form of this drug to **reduce gingival inflammation**
- Because of its high toxicity we can't use a high concentration of this drug or for a long period of time, it can cause : **GI bleeding , CNS toxicities, mental confusion, diarrhea, and frontal headache.**

OXICAM DERIVATIVES

- They include: **piroxicam** and **meloxicam**
- They are used to treat: **RA, ankylosing spondylitis, and osteoarthritis**
- These derivatives have **long half-lives,** so they make it easier to administer this drug when we have problems with compliance, and the parent drug as well as its metabolites are renally excreted in the urine.
- **Meloxicam** inhibits both COX-1 and COX-2, with *preferential binding* for COX-2, and at low to moderate doses it has less GI side effects than **piroxicam.**

FENAMATES

- **MEFENAMIC ACID: which is a fenamate derivative**

- They are used for menstrual pain
- They do not have any other advantage over NSAIDs as anti-inflammatory agents
- They have some disadvantages: like side effects including, **diarrhea and hemolytic anemia** in a small population of patients.
- These drugs are not preferential to be used as the *first choice for the treatment of inflammatory conditions.*

HETEROARYL ACETIC ACIDS

- They include: **diclofenac, tolmetin, and ketorlac**
- These drugs are **inhibitors of COX-1**
- These drugs are approved for long term treatment of **rheumatoid arthritis and osteoarthritis**
- **Diclofenac** is more potent than **indomethacin or naproxen**
- An **ophthalmic** preparation is also available
- *Diclofenac* accumulates in synovial fluid, this is beneficial in the treatment of inflammation affecting the joints, and the **primary route of excretion** for the drug and its metabolites is the kidney

DICLOFENAC SODIUM

- It can be given: **orally, injection and cream**
- Used orally: 50mg after food
- Used I.M (injection): 75mg
- There is a newer form: Diclofenac *potassium,* it has a quicker absorption which results in a quicker respond, while the Diclofenac *sodium* has delayed release
- Pregnancy: Category C
- Toxicity similar to others

COMMON ADVERSE EFFECTS of NSAIDs

- Platelet dysfunction
- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
- Acute renal failure in susceptible patients
- Sodium + water retention and edema
- Analgesic nephropathy
- Prolongation of gestation and inhibition of labor
- GIT bleeding and perforation

ACETAMINOPHEN

- It is an **analgesic**
- It inhibits the production of prostaglandins
- Mainly works in the **CNS**
- It has **antipyretic and analgesic properties, but has WEAK anti-inflammatory activity**
- It does not affect platelets
- **It is the safest drug to be used in pregnancy**
- It is the drug of choice for children under the age of 15 who have a viral illness
- It's very gentle on the GI, does not cause GI irritation
- **Toxicity associated with this drug: HEPATOTOXICITY,** because of this toxicity it causes death of hepatocytes, and if the overdose is not treated quickly within 12 hours, it may cause death in the overdosed patient
- It is a substrate for **cytochrome p450**
- At normal doses of acetaminophen, there will be a production of one metabolite called: **N-acetylbenzoiminoquinone, which is highly reactive and potentially dangerous and toxic,** our body tries to get rid of this toxic metabolite through the glutathione system. When taking an overdose of acetaminophen, there will be an accumulation of this toxic metabolite, this metabolite attaches to the sulfhydryl group of glutathione , forming a nontoxic substance.

QUESTION: WHAT IS THE MAXIMUM DOSE A PERSON CAN TAKE OF ACETAMINOPHEN?
8 pills, over 4g or 400mg, signs of liver toxicity will be present.

TEST YOURSELF:

1. Mechanism of action: aspirin-platelet effects:

a. Promotes platelet aggregation
b. Activates thromboxane synthesis
c. Both
d. Neither

2. Effective in managing acute gouty arthritis and ankylosing spondylitis; also accelerates closure of patent ductus arteriosus in premature infants:

a. Ketorolac
b. Phenylbutazone

c. Methotrexate
d. Indomethacin

3. Drug associated with the hepatic/renal toxic metabolite: N-acetylbenzoiminoquinone:
   a. Indomethacin
   b. Acetaminophen
   c. Aspirin
   d. Diclofenac

4. Your ten year old son is running a fever of 101 F after developing a cold. To help him feel better you go to the local pharmacy to purchase a fever-lowering medication. However, as a good parent you recall that there are warnings about the drug-induced Reye's syndrome in children given the wrong type of NSAID. Which NSAID is associated with this potentially serious condition?
   a. Acetaminophen
   b. Aspirin
   c. Celecoxib
   d. Montelukast

5. Which of the following drugs is a propionic acid derivative?
   a. Ibuprofen
   b. Phenylbutazone
   c. Indomethacin
   d. None of the above

6. The enzyme involved in the therapeutic action of NSAIDs is:
   a. Cyclo-oxygenase
   b. Cytochrome
   c. Monoamine oxidase
   d. Lipocortin-1

Answers: 1. D 2. D 3. B 4. B. 5. A. 6. A