- بسم الله الرحمن الرحيم -

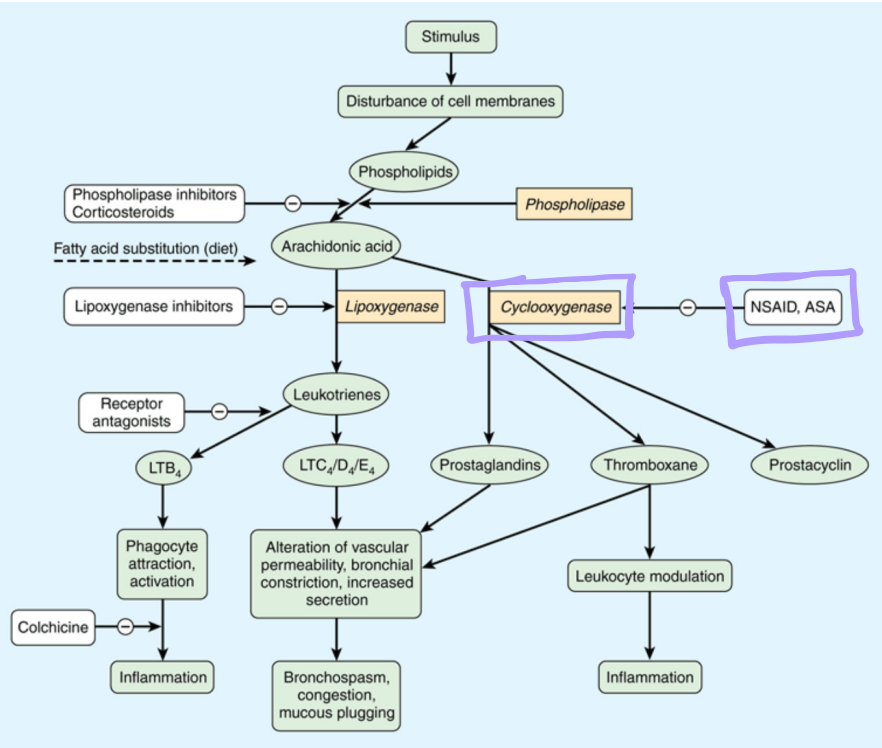
" وما أوتيتم من العلم إلا قليلا "

Pharma - NSAIDs (2)

In the previous lecture we talked about a brief introduction of NSAIDs and how they modulate the inflammatory pathway (remember COX-1/COX-2 and their roles in physiological and pathological situations), these two enzymes are blocked by NSAIDs (both are blocked by nonselective NSAIDs, some types of them exhibit some preference toward one of COX enzymes).

In this sheet we will talk about specific examples of NSAIDs

In general, al NSAIDs are non selective while we have noticed that recently they have little bit more selectivity or we probably concluded that from side effects associated with the reuse.



Now will talk specifically about some drugs 💊🔬

1. Aspirin

A. The prototype of NSAIDS it is very old drug, it was used centuries ago, actually it is derived from a tree شجرة الصفصاف that gives us salicylic acid, It is the most commonly used NSAIDs, all new drugs of this group will be compared with aspirin.

في الحضارات القديمة كانوا يستخدموا لحاء شجرة الصفصاف ليروحوا الألم ومع تقدم العلم تم اكتشاف انه المادة في اللحاء هي عبارة عن salicylic acid و الأسبيرين هو عبارة عن هاد الحمض الضعيف وضافوله مجموعة استيل صناعيًا فصار اسمه acetylsalicylic acid

Do you remember what makes aspirin distinguished from NSAIDs?! The difference is related to aspirin therapeutic or pharmacological effect that it is the only agent that has anti platelets effect and regarding to its selectivity (it prefers COX-1 but still it's non selective). Also aspirin is irreversible

B. When we are asked about the pharmacological mechanism of aspirin : it is non-selective irreversible inactivator of COX-1 & COX-2 ..... it's very important to know that 🔥🔥🔥

C. Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.

The effect of all NSAIDs including Aspirin is inhibiting the production of prostaglandins, hmmmmmm!!!!
So why we said in the previous lecture that they give different effects.
يعني هم كلهم بيشتغلوا عن طريق انهم يوقفوا تصنيع ال prostaglandins فكيف بتلاقي دوا معين منهم بقلل الحرارة ودوا تاني بيوقف ال congestion

In which cases aspirin works and How aspirin works in these cases?!

1. Analgesia:

- for being analgesics, decreasing prostaglandin synthesis will prevent the sensitizations of pain receptors for chemical and mechanical stimulus.
- Some studies have shown that aspirin can depress pain by having stimuli in certain subcortical regions in the brain.

2. Temperature/ fever (antipyretic):

First, let's talk about how temperature increases during inflammation 🔥
We have the production of PGE2 is stimulated by → IL- 1 which is responsible for resetting the (set point of temperature) through the thermoregulatory center in the hypothalamus, so it increases the set point, so when aspirin prevents PGE2 it lowers (resets) the set point of temperature (back to the normal), but it has no effect on normal body temperature. That was the first mechanism of lowering the temperature.
يعني اذا كانت الحرارة ٣٩ برجعها لل ٣٧ .... بس اذا اخذنا الدوا و حرارتنا ٣٧ اصلا ما اله اي تأثير عالحرارة
The second mechanism:
The aspirin has the ability to cause peripheral vasodilation which will cause dissemination of heat from the skin through sweating.

لو سمحت تقرأ هاد الجزء بتركيز لمرة أو مرتين 🧠
احنا حكينا إنه الأسبرين بشتغل خافض للحرارة بطريقتين الأولى إنه بوقف تصنيع PGE2 اللي
أساسا مسؤول عن تصنيعه IL-1 اللي بشتغل عمركز تنظيم الحرارة في تحت المهاد
hypothalamus فبيعمل الاسبرين على ايقاف هاي العملية وبالتالي بمنع رفع درجة الحرارة
أما الطريقة الثانية إنه بعمل على توسيع الأوعية الدموية فبمر فيها دم اكتر و بصير تضييع لحرارة
الجسم الداخلية عن طريق التعرق
الطريقة الثانية خاصة فقط بالأسبيرين دونا عن باقي ال NSAIDs
طب وشو الفائدة من هاد الحكي كله ؟!
الفائدة إني بدي ألفت انتباهك انه توسيع الأوعية الدموية مش بس بطير الحرارة ... كمان هو بعمل
على تقليل ضغط الدم وهو شيء خاااااص للاسبيرين بسبب وجود نظام *تطبير* الحرارة عن
طريق التعرق وتوسيع الأوعية الدموية ، أما فيما يخص باقي NSAIDs فهي لا تملك هذا النظام
بل تسبب Vasoconstriction يعني راح يزيد ضغط الدم
كيف بتسوي vesoconstriction عالهامش، عن طريق انها بتوقف تصنيع ال PGs اللي بتعمل
توسيع الاوعية الدموية لبصير الconstriction لكن ما عندها نظام توسيع الاوعية الدموية عشان
تطير الحرارة ... فالكفة الراجحة بتكون نحو التضييق ..... ومن هنا نستنتج ✍️

Hypertension is contraindication of NSAIDs except ASPIRIN 💊 don't forget that please!

how "aspirin" causes vesodilation ?!

It has direct relaxing effect in vascular smooth muscle cells (VSMC) in the peripheral blood vessels that's why it causes vesodilation and leads to decrease body temperature

Remmember

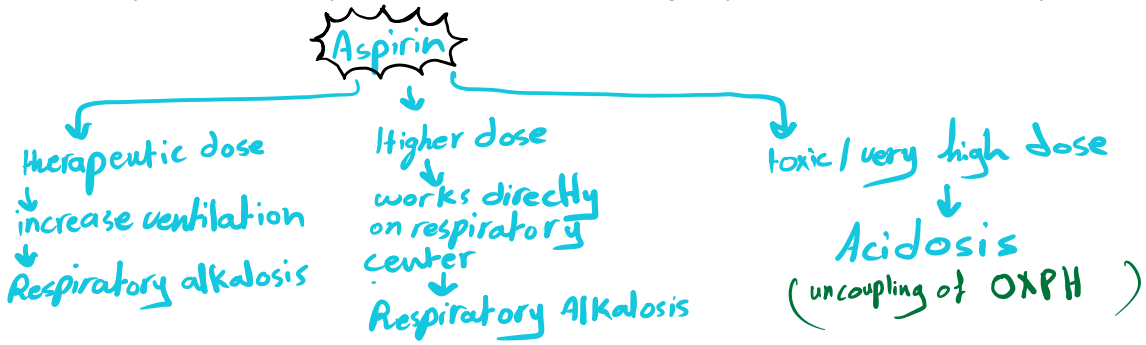
Aspirin has no effect on normal body temperature

لحد هسا إحنا حاكيين إنه الأسبرين

1. Analgesic 2. Antpyretic

3. Effects on respiratory system: mainly effects on pH

-Initially, at therapeutic doses, aspirin increases alveolar ventilation.
Increasing ventilation → We will lose CO2 → Respiratory Alkalosis
Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis



When we increase the dose more and more we move from respiratory alkalosis toward metabolic acidosis due to different mechanisms

Toxicity of salicylates → High dose not therapeutic dose

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis
- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, عشان هيك اللي عنده Aspirin toxicity بترتفع درجة حرارته increased glyconeogenesis, and increased heat production
- ✱ (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids → This will stimulate lipid and amino acids metabolism → cause metabolic Acidosis
- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

قد يسأل سائل منكم شو علاقة الـ toxicity بالـ respiratory effects؟ زي ما اتفقنا إنه التنفس مرتبط ارتباط وثيق بالـ pH (نشاة فضة إنزاع CO_2) و أسباب الـ toxicity متعلقة metabolic disorders اللي بتسبب Acidosis

-This toxicity can happen a lot especially for little children.
-We have in the pharmacies something called baby aspirin 100mg or 81mg (low dose), this is the one that adults use prophylactically because of its anti platelets activity to prevent thrombosis or embolism, some people have history of thrombosis or thrombotic events include myocardial infarction, strokes or any thromboembolic disease will use this baby aspirin.
-Aspirin is not recommended for children…… it causes hepatotoxicity and problems in the brain (Rey's syndrome)

متى بنضطر نعطي الأطفال أسبرين ؟ لما يكون عليهم حرارة يعني التهابات بشكل عام وتحديدا التهابات القناة التنفسية
وشو أغلب أسباب التهابات القناة التنفسية ؟ فايروسات

Recently we have found that there is increased incidence of Rey's syndrome which characterized by damaging of the liver and the brain in children under 12 years old if they have a viral infection.
CONTRAINDICATION of aspirin:
Child under 12 years old with viral infection, we don't use aspirin or any salicylate

⊘ كتير منه toxicity و الناس كانو بيعيس معهم baby Aspirin بالزمنات كانو

HOW TO TREAT THIS TOXICITY ?

1. We have high fever, we should cool the patient.
2. We should correct the acidosis by alkalization of urine.
3. Fix the electrolytes balance

There are some people who have salicylic acid allergy, we call this condition salicylism, we should take care of these individuals, salicylate is not found in aspirin only, there are other products and drugs that contain salicylate.

هسا إحنا حكينا عن أثار الإسبرين ؟

1. Analgesic 2. Antipyretic 3. respiratory alkalosis → toxicity ... metabolic acidosis

4. GI system effects associated with prolonged use of NSAIDs

Why patients are recommended to take aspirin and other NSAIDs after eating? because these drugs are stomach irritant through prevent the synthesis of PGE2 which is responsible for mucus secretion so the protective layer of stomach will be remove also PGE2 inhibits acid secretion, the continuous use of these drugs may cause peptic ulcer.
We can treat this problem by using a group of drugs:
A. Agents used for the prevention of gastric and/or duodenal ulcers include proton-pump inhibitors (PPIs); esomeprazole, lansoprazole, omeprazol (prototype). They all work by inhibiting acid secretion.
B. Other drugs can be used like histamine antagonists, histamine receptors are H1 and H2 (the main one in the stomach, if we inhibit it we inhibit acid secretion from parietal cells.
C. Prostaglandin analog like misoprostol it mimics the action of prostaglandins in stomach, so we can take it along with aspirin, this drug is used in abortion because it causes uterine contraction like the natural PGs.
At stomach pH, aspirin is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing direct damage to the cells. Changing the route of administration will cause the same stomach irritation.

5. Effects on the platelets aspirin is the one that has anti platelets activity so it ia thought to be more selective towards COX-1 which is responsible for the production of thromboxane A2 TXA2 which leads to production of thrombosis.
#TXA2 enhances platelet aggregation >> Low doses 81 mg daily of aspirin can irreversibly inhibit thromboxane production in platelets via acetylation of cyclooxygenase.
#Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (7 days to 10 days)>> As a result prolonged bleeding time.
If we prepare a patient who takes aspirin for a surgery we should wait a week to get rid from aspirin, if we don't wait the patient will suffer from bleeding.

6. Effects on kidney :

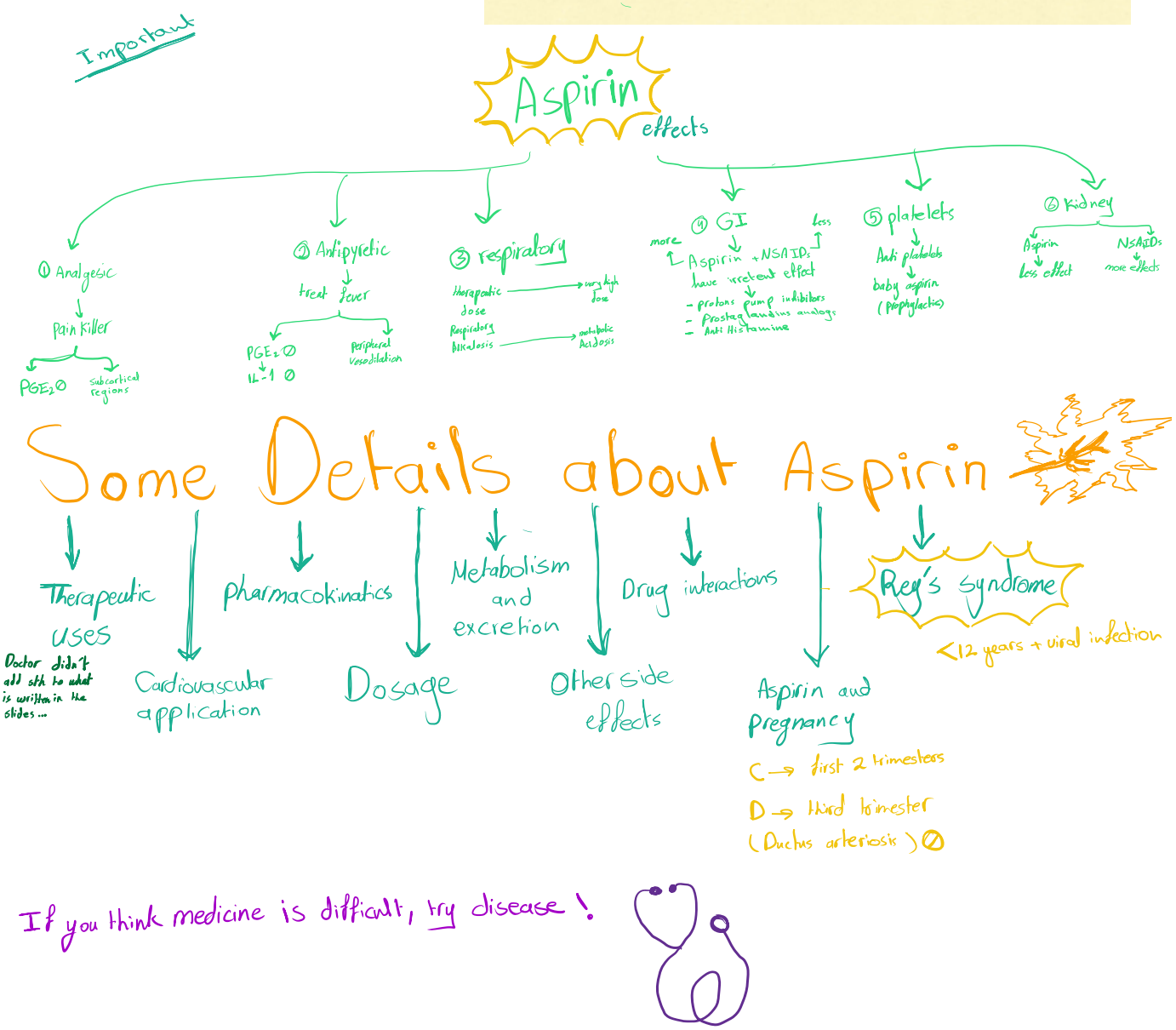
aspirin has lesser effect on kidney than other NSAIDs (less nephrotixic effects).

Effects of NSAIDs on kidneys:

1. Retention of urine flow causing: a. Edema , b. Hyperkalemia
2. Arterioles contraction (afferent blood vessels constriction) that leads to the stimulation of renin-Angiotensin system and that will cause hypertension.

As a summary, most of NSAIDs have detrimental effects on the kidneys.
Aspirin has less effects, especially low dose aspirin (baby aspirin) anti platelets, that is used as prophylactic agent in 81 or 100 mg.
81-300 mg aspirin dose still has anti platelets, COX-1 selective activity.

Do you remember how renin-angiotensin works?! Actually it causes hypertension. Renin–angiotensin system (RAS), or renin–angiotensin–aldosterone system (RAAS), is a hormone system that regulates blood pressure, fluid and electrolyte balance, and systemic vascular resistance.



If you think medicine is difficult, try disease !

Therapeutic uses

- The salicylic acid derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA. → Rhematoid Arthritis
- Commonly treated conditions requiring **analgesia** include headache, arthralgia, and myalgia.

External applications:

- Salicylic acid is used topically to treat corns and warts.

Cardiovascular applications:

- Aspirin is used to inhibit platelet aggregation. Low doses are used **prophylactically** to
- reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death
- Studies have shown a reduced risk of death in those having an acute **myocardial infarction** and engina attack (ذبحة صدرية)

necrosis of cardiac tissue

Causes
- vasospasim of blood vessels
- Athero sclerosis (Deposition of lipids in the blood vessels)

PHARMACOKINETICS

Administration and distribution:

- After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine**
- **Rectal** absorption of the salicylates is **slow** and unreliable, but it is a useful route for administration to vomiting children.
- Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent **Reye's** syndrome. Doctor said 12 but it can happen in older people.
- Salicylates are highly protein bound the protein that carries most drugs (Albumin)

The aspirin must not be use with
1. **Phenytoin**
2. **Warfarin**
3. **Valproic**

because they are all bound to albumin if we administered aspirin with phenytoin, aspirin will be bound and the free dose of phenytoin will increase (the unbound form) this will cause toxicity.

Dosage:

The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity .

may reach 1000 mg → pay attention to its harmful effects on GIT

- For example, two 325-mg aspirin tablets administered four times daily produce **analgesia**, whereas 12 to 20 tablets per day produce both analgesic and **anti-inflammatory** activity.

① thromboembolitic events ② transient ischemic attack

- For long-term **myocardial infarction prophylaxis**, the dose is 81 to 162 mg/day
- for those with **RA or osteoarthritis**, the initial dose is 3 grams/day

After this value Aspirin will lose its selectivity

- for **stroke prophylaxis**, the dose is 50 to 325 mg/day

Metabolism and excretion

في رحلة العمر والأيام
مسرعة ...
لا تنسَ من أنت أو ما وجهة
السفر ...

- At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood .
- Salicylate is converted by the **liver** to water-soluble conjugates that are rapidly cleared by the **kidney**
- Both **hepatic** and **renal** function should be monitored periodically in those receiving long-term, high-dose aspirin therapy. If we have renal disease we can't use Aspirin for a long period, NSAIDs as well.
- aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

Other side effects

Hypersensitivity: Approximately 15 percent of patients taking *aspirin* *experience hypersensitivity reactions*.

There are some people who face Aspirin over dose toxicity and have milder reaction of Salicylism

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

we have CNS side effects of Aspirin :-
① balance lost. ② tinnitus طنين الأذن

Reye's syndrome: children are given Ibuprofen / paracetamol instead of aspirin in this case ...

- Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. encephalopathy
- This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin

Drug interactions:

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

gout — NSAID — anticpileptic

- Concomitant use of **ketorolac** and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

Don't mix two NSAIDs together, this will not enhance the pharmacological efficacy, rather it would exaggerate the side effects.

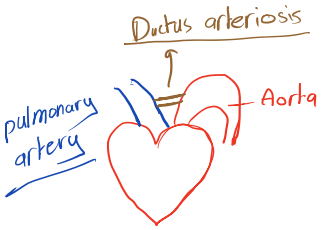
Aspirin and pregnancy

- In pregnancy: Aspirin is classified as FDA pregnancy category C risk during Trimesters 1 and 2
  ① help the fertilized ovum to be implanted in the uterus
  ② Aspirin causes vasodilation in the uterus, more blood reach to the embryo
- category D during Trimester 3.
  to keep ductus arteriosis open
- Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breast-feeding.
  let it to the judgment of doctor

FDA Pregnancy Categories

Category	
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Source: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (Federal Register/Vol. 73, No. 104/Thursday, May 29, 2008) This additional table is not required * Added by the writer



During the embryonic life ... Aorta was linked to the pulmonary artery through Ductus Arteriosis, this duct is very important it shouldn't be blocked ... prostaglandins keep it open So, the women shouldn't take aspirin.

There is an abnormality when the Ductus Arteriosis isn't closed After birth → in this case we give the baby Ibuprofen / indomethacin. (NSAIDs)
If it isn't closed after 2 weeks we should do a surgery.

Reye's syndrome

This can happen without aspirin, aspirin increases the incidence.

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 a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

Aspirin ... Done

مش راح نحكي من اللي جنبهم ⊘
الدكتورة ما حكت عنهم ...

2. Other NSAIDs

① propionic acid derivatives
1. Ibuprofen] same
2. Naproxen]
3. ketoprofen ⊘
4. fenoprofen ⊘
5. flurbiprofen ⊘

② Acetic Acid derivatives
1. indomethacin
2. Sulindac ⊘
3. Etodolac ⊘

③ oxicam derivatives
1. piroxicam
2. Meloxicam

④ fenamates
1. Mefenamic

⑤ Heteroaryl acetic acid

Propionic acid derivatives

- **Ibuprofen , naproxen, fenoprofe, ketoprofen , flurbiprofen**

- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- their **GI** effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases

- All are well **absorbed** on oral administration and are almost totally bound to serum **albumin**. Don't mix 2 NSAIDs
- They undergo **hepatic** metabolism and are excreted by the **kidney**.
- The most common adverse effects are **GI**, ranging from dyspepsia to bleeding. peptic ulcer.
- Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported + reversible loss of hearing

↑Acid

. The use of sulindac has also been linked to cases of acute pancreatitis.The use of dimethylsulfoxide (DMSO) topically in combination with sulindac has been reported to induce severe neuropathies → vehicle

Naproxen and Ibuprofen

- Pregnancy : category C, category D from 3 trimester → mainly due to Ductus Arteriosis
  first 2 trimesters
- Increase the risk of cardiovascular thrombotic event, MI and stroke. maybe due to its preferance of cox-2 pathway.
- Increase risk of GI bleeding.
- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.
- Asthmatic patient. Contraindication

Acetic acid derivatives

the most dangerous NSAIDs – have serious side effects

- **Indomethacin , sulindac , Etodolac**
- All have anti-inflammatory, analgesic, and antipyretic activity. They act by **reversibly** inhibiting cyclooxygenase.
- 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.
- **Etodolac** has effects similar to those of the other NSAIDs

Indomethecin → Closes Ductus Arteriosis After birth

- **acute and chronic rheumatoid arthritis and osteoarthritis.**
- **Also useful in ankylosing spondylitis, acute gouty arthritis, bursitis, and tendinitis.**
- **Side effects:**
  - **It produces more CNS side effects than most of the other NSAIDs. Severe headache occurs in 25 to 50% of patients; vertigo, confusion, and psychological disturbances**
  - **GI symptoms also are more frequent.**
  - **Hematopoietic side effects (e.g., leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, and agranulocytosis**
  - **Ocular effects (blurred vision, corneal deposits) Hepatitis, jaundice, pancreatitis, and hypersensitivity reactions** Rare

we have other anti inflammatory drug (phenylbutazone) that is associated with agranulocytosis

Oxicam derivatives

- ***Piroxicam*** *and* ***meloxicam***
- *are used to treat RA, ankylosing spondylitis, and* osteoarthritis.
- They have **long half-lives**, which permit once-daily administration, 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 shows less GI irritation than *piroxicam.*

we use paracetamol 4 times per day

we use Aspirin 3 times per day

long half-lives help us to achieve better compliance

Fenamates ①

- ***Mefenamic***
- *have **no advantages** over other* NSAIDs as anti-inflammatory agents.
- Their side effects, such as **diarrhea**, can be severe, and they are associated with inflammation of the bowel.
- Cases of hemolytic anemia have been reported

Heteroaryl acetic acids ②

- ***Diclofenac and tolmetin , ketorlac***
- *are approved for long-term use in the treatment of RA,* osteoarthritis.
- ***Diclofenac** is more potent than indomethacin or naproxen.*
- *An **ophthalmic** preparation is also available.*
- *Diclofenac accumulates in synovial fluid, and the primary route of excretion for the* drug and its metabolites is the **kidney**.

Diclofenac sodium ③

- Used PO 50mg after food, I.M. inj 75mg
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Pregnancy: category C

Diclofenac sodium ④

- **C/I**
- Hypersensitivity.
- Asthmatic patient.
- Patient with history of peptic ulcer.
- Metabolism: liver.
- Excretion: urine.

The doctor didn't say anything about these slides in this lecture ... Some informations about them maybe mentioned in the next sheet.

3. COX-2 inhibitors

Selective COX-2 inhibitor

Celecoxib, Rofecoxib → Drawn from the markets

- more selective for COX-2 than for COX-1. → Causes myocardial infractions and strokes.
  ↓
  because we switched the arachadonic acid from Cox-2 pathway towards Cox-1 pathway that is responsible for thromboxane A_2 formation that enhances the thrombosis.
- Adverse effects are slighter than other NSADs.
- Long-term studies of the incidence of clinically significant gastrointestinal ulcers and bleeding are not yet completed.
- May increase the incidence of edema and hypertension.

* we invented cox-2 inhibitors to get rid from GI irretation that limits the usage of NSAIDs.

* it has the black box warning. Due to hypertension and thrombosis.

اللهم صل وسلم وبارك
على سيدنا محمد وعلى آله وصحبه
أجمعين