Pharmacology

Doctor 2017 | Medicine | JU

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1st system - MSS

In this part of the course, we are going to be talking about: *0-10 mins*

- Anti-inflammatory Drugs.
- Muscle Relaxants.
- Anti-hematuria Drugs.
- Anti-gout Agents.
- Drugs affecting the Skin.

We will be talking mainly about the Anti-inflammatory drugs which are mainly related to the Musculoskeletal System because it's a common site of inflammation, mainly Rheumatoid Arthritis and Gout.

Anti-inflammatory drugs are used to combat inflammations, and they are divided into 2 types:

- Steroids (The Magical Drug) – because it's given in many cases. They have many hormonic effects as they are hormones. We will cover them mainly in the Endocrine System (in the summer course). When in doubt, give steroids.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) – Very big group of drugs that are used commonly and nearly everyone is aware of their uses. (Paracetamol [Panadol] – Aspirin – Profin – Diclofenac [Voltarin] and a lot of other drugs).

Terms and Definitions:

1- Analgesics [an = without, algia = pain]:

Drugs used to relieve (reduce) pain, they act in various ways on the Central and Peripheral Nervous Systems. They include:

a. NSAIDs – For mild to moderate pain.
b. Opioids – Reduces severe pain. (we'll talk about them next year in details)
c. Cannabinoids – Recently used in Jordan for severe pain.

2- Anti-inflammatory:

Property of a substance or treatment that reduces inflammation.

3- Anti-pyretic:

Prevents or reduces fever by sending signals to the temperature center in the body (the hypothalamus), resetting it to the original temperature of 36.9C. Does not affect normal body temperature.

4- Addiction:

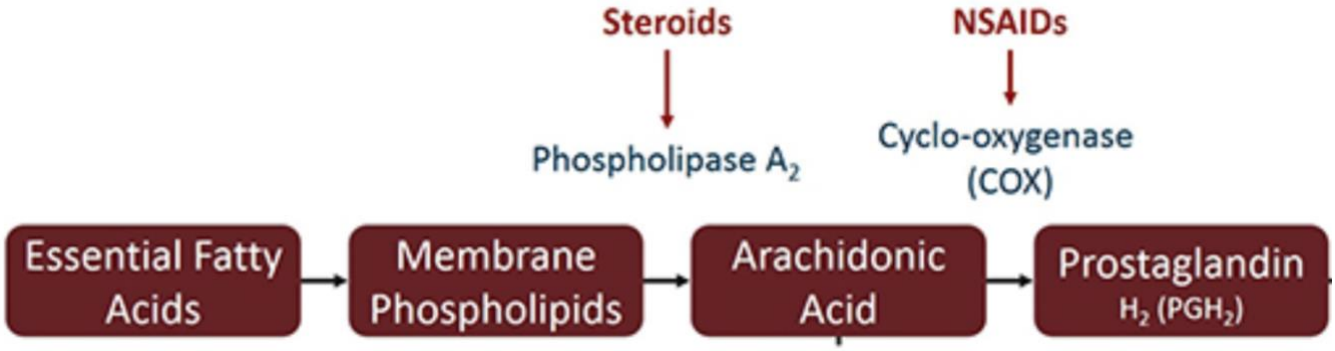
Dependence on a substance (Alcohol, drugs) to the point that it's very difficult to stop taking them and causes physical and mental reactions.

NSAIDs:

Inflammation, pain and fever are all linked to prostaglandins, so affecting the prostaglandins will have an effect on those three. So the NSAIDs have analgesic, anti-pyretic and anti-inflammatory effects all at the same time. Ex, Profin could be used to relieve pain, inflammation or even to reduce fever.

This effect is caused by the inhibition of our old friend, the Cyclooxygenase. The long pathway from membrane phospholipids to Arachidonic Acid results in the production of Prostaglandins which induce -not only- inflammation, but also pain (hyperalgesia) and also goes to the hypothalamus resulting in the elevation of body temperature (fever). The NSAIDs inhibit the cyclo-oxygenase (COX), thus arresting the process before resulting in those prostaglandins and thus inhibiting their effects.

10-20 mins



Types of Cyclooxygenase:

There are 3 types of cyclooxygenase enzymes:

COX-1: Wide spread, constitutive (always on) and important in tissue homeostasis. It is important for the GI tract and stomach protection from its high acidity by reducing secretions. They also affect thrombosis and platelet aggregation.

COX-2: Induced in inflammatory cells by inflammatory mediators. It's the main target we try to affect.

COX-3: A splice variant of COX-1, we aren't interested in it right now.

The main problem is that NSAIDs don't have great selectivity for only COX-2, it affects COX-1 and inhibits them. Those widespread drugs thus have lots of side effects and aren't that great, despite them being well-known and being over the counter drugs (given without a prescription and in market outlets). Their main side-effect is Ulcers and GI disturbances.

Effects of inhibiting cyclooxygenase:

1- Antipyretic: NSAIDs inhibit PG (Prostaglandin) production in hypothalamus - which contains center for normal body temperature regulation – and "reset" the temperature.
   During inflammation, IL-1 increases Prostaglandin E synthase (PGE) resulting in the increase of the body temperature set point. COX-2 is increased also by IL-1 and increases the production of PGE2.

2- Analgesic effect: (reduction of pain associated with inflammation)
   Prostaglandins sensitize pain receptors to the inflammation mediators.

3- Anti-inflammatory: (modification of the reaction)
   Due to the action of COX-2 (NSAIDs, PGs, and TX synthesis in inflamed cells)
   a. Decrease: vasodilation, cell adhesion and migration, stabilizes lysosomes.
   b. Decrease Vascular permeability and thus Edema.

20-30 mins

Doses of NSAIDs:

The regular dose of NSAIDs induce the first and second effects (Analgesic & Antipyretic) because they are a reflection (result) of an inflammation, while in an inflamed region, the activation of COX-2 is very high so you need a high dose of NSAIDs to really re-inhibit the high concentration of COX-2. Ex. Arthritis patients take large doses of Aspirin or Profin to reduce the inflammation (usually 3 times the normal dose of the Analgesic or antipyretic dose). That's why you can find Profin 200mg, Profin 400mg and Profin 600mg. Same with Diclofenac too and many other NSAIDs.

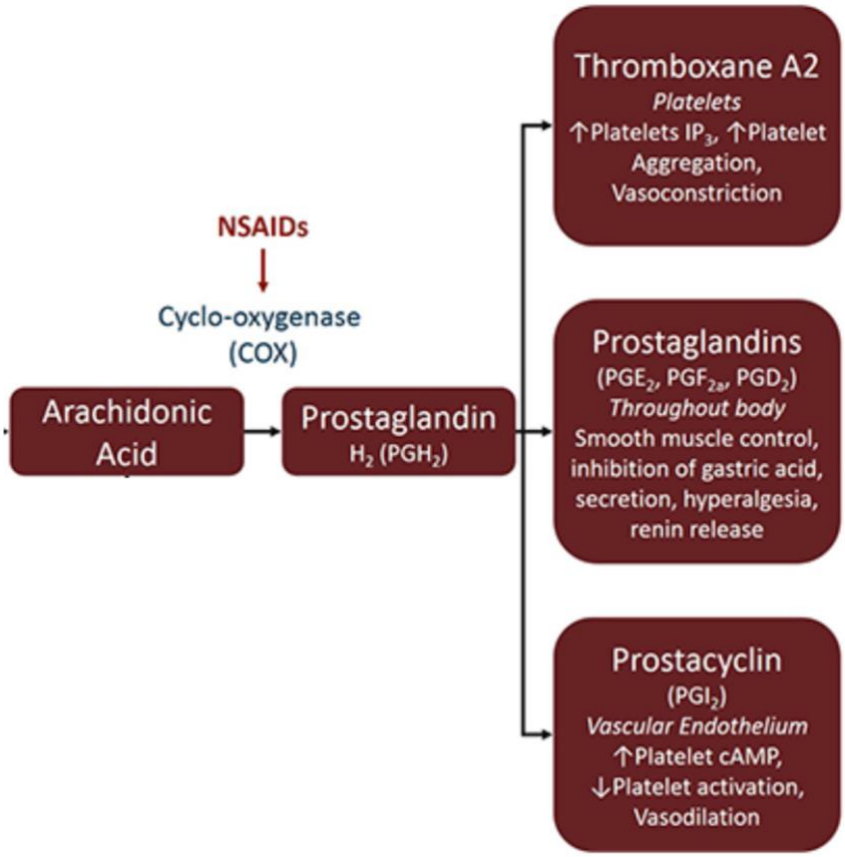
**Remember that:
Low dose: Mild Pain & Fever – Regular dose: Moderate Pain & Fever.

High dose: INFLAMMATION
for severe pain we use Opioids or Cannabinoids.

Effects of Prostaglandins:

Prostaglandins result in many diverse effects on the body like Smooth muscle control, inhibition of gastric acid secretion, hyperalgesia and renin release.

Also, a part of the prostaglandins that result from COX-2 is Thromboxane A2, it induces the platelets IP3 secretion, platelets aggregation and also Vasoconstriction. So when COX-2 is inhibited, you can inhibit the secretion of Thromboxane and thus inhibit thrombosis. Even though, to get this effect, you should inhibit this mechanism continuously. Thromboxane is synthesized and stored in vesicles inside the platelets which makes it hard to control it. So for a full inhibition, you need to give a drug that binds irreversibly to COX-2. That's because when you use a reversibly binding drug, the thromboxane will be secreted when a stimulus comes in. Our friend Aspirin is the only drugs in all of the NSAIDs that binds irreversibly to COX (1 and 2) by acetylation (covalent bonds). This results in completely stopping the synthesis of Thromboxane A2 resulting in the inhibition of the aggregation process. That's why Aspirin is very common between people (Baby aspirin 80mg) which is a low dose that's sufficient with very little side effects. It's a great drug that most people use even without a disease requiring it. Regular Aspirin dose is 325mg per tablet. It's used for analgesia and fever, while inflammation requires using 3-4 tablets of the regular aspirin.



NSAID Classification:

The table is not for memorization, but it's good to know its details. *30-40 mins*

Chemical differences between these drugs isn't what we are concerned with.

Diclofenac is commonly known as Voltaren.

Out of these drugs, 16 are currently used nowadays in a daily routine. Diclofenac (Voltaren) is the most famous one of them in Jordan.

NSAID Classification

Nonselective COX inhibitors

Acetic acid
Diclofenac
Etodolac
Indomethacin
Sulindac
Tolmetin

Fenamate
Meclofenamate
Meclofenamic acid

Naphthylalkanone
Nabumetone

Oxicam
Piroxicam
Meloxicam

Propionic acid
Fenoprofen
Flurbiprofen
Ibuprofen
Ketoprofen
Naproxen
Oxaprozin

Salicylate
Aspirin
Diflunisal

Choline magnesium trisalicylate
Salsalate

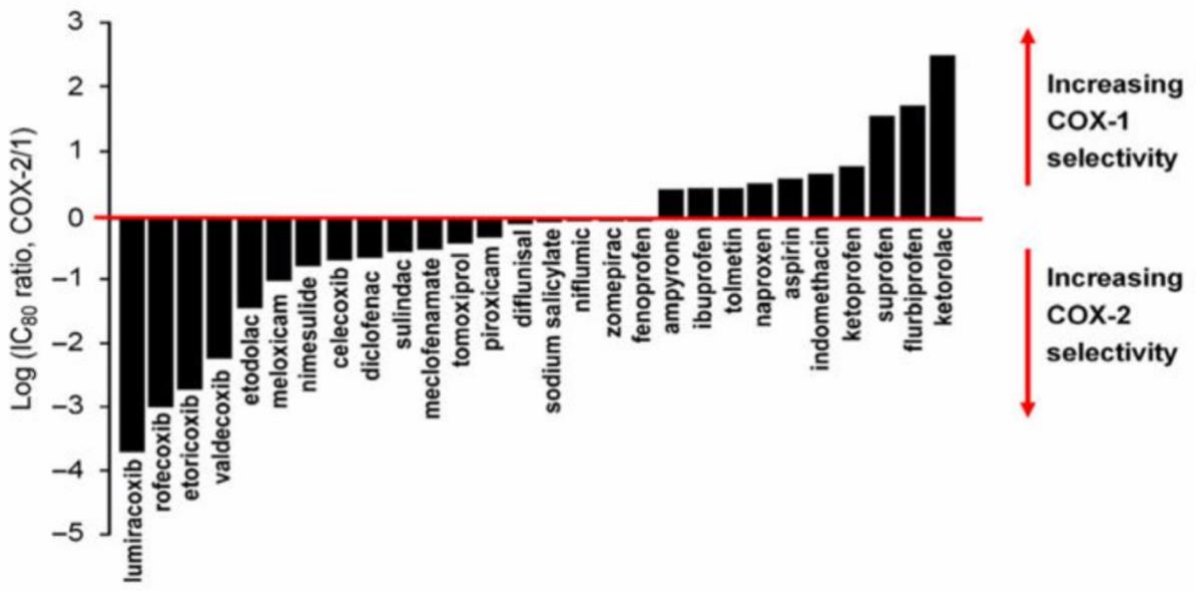
Selective COX-2 inhibitors
Celecoxib
Rofecoxib

Out of the Selective COX-2 inhibitors, Celecoxib is the most important one that we need to know about, it's known in Jordan under the name Celebrex. It's very famous and it's used with people that have Peptic Ulcers and people with kidney complications. That's because COX-1 produces prostaglandins in the kidney that work on the efferent arteriole making it dilate, and when the PG synthesis is inhibited, this causes constriction of that arteriole. This causes the glomerular filtration rate (The rate in which the blood gets into the kidney) to decrease. This effect is not visible on normal people, but people with Kidney complications and obstructions are not allowed to take NSAIDs that affect the COX-1 (Nonselective COX Inhibitors). Also people who have hypertension and do take hypertensive drugs, their intake of NSAIDs counteracts their effect rendering them useless because of its effects on the kidney.

Selective COX-2 inhibitors were thought to be good for these people but they were then discovered to have dangerous effects on the Cardiovascular system causing myocardial infarction in some cases. It's thought that between the selective COX-2 inhibitors, Celecoxib is the one with the least side effects but that doesn't mean that it's still safe for use.

NSAIDs have their side effects but we cannot stop using them mainly for their analgesic effects. Pain is the main reason people admit to hospitals and they need to relieve it, and you cannot give Opioids like Tramadol/Heroin which are clearly more dangerous and risks addiction. So you usually give paracetamol or NSAIDs.

COX Selctivity:



This Diagram is a proximate demonstration of how drugs are selective to either COX-1 or COX 2 compared to each other. It's not for memorization but it shows us how they vary in selectivity. Notice mainly that the most selective drugs to COX-2 are the coxibs (on the left side of the diagram), otherwise most of the other drugs do bind to both but on different scales. Etodolac binds to COX-2 more than COX-1 that's why it's linked to less GI disturbances.

Also notice that the main drugs that you find over the counter (Aspirin, Ibuprofin and Ketoprofin) are on the right-side of the diagram, shifting towards the selectivity of COX-1, shifting towards the main side effects (GI distress).

Aspirin:

Was first isolated in 1829. It is the most commonly used anti-inflammatory agent (other agents compare to it). However, about 15% of patient show intolerance to Aspirin, And some of the newer NSAIDs are superior to Aspirin and cause less gastric irritation, and/or they can be taken less frequently.

Aspirin is unique in the ability to acetylate the cyclooxygenase (irreversible bond). Other NSAIDs are reversible inhibitors of cyclooxygenase.

That was where the doctor stopped, he just read this slide and ended the lecture

Good Luck Everyone!!