Pharmacology

Doctor 2017 | Medicine | JU

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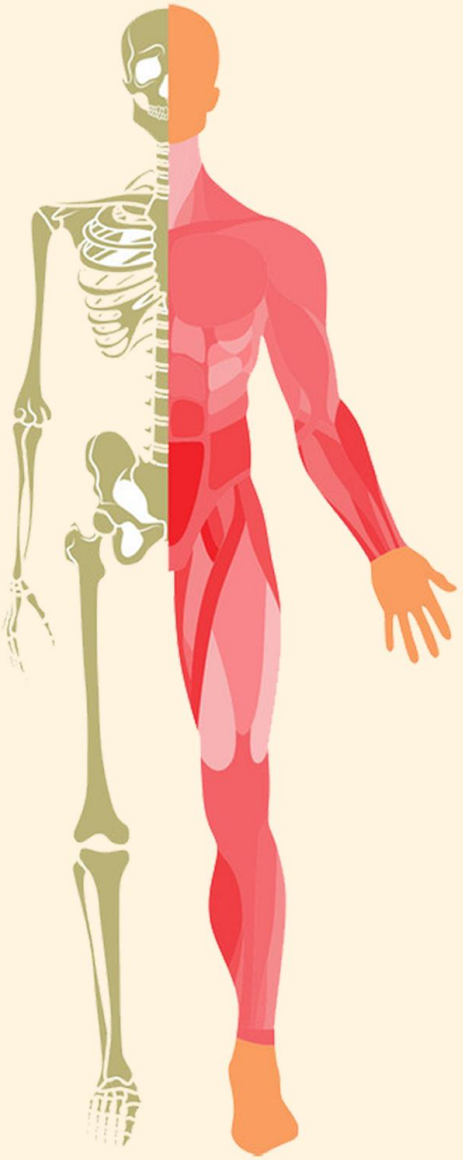

1st system - MSS

Pharma lecture 2

First of all sorry for being late but I took lecture 1 yesterday and I even didn't take lecture 2 so I wrote it from the video which was uploaded on YouTube.

In the previous lecture the Dr. talked about NSAIDs (non-steroidal anti-inflammatory drugs) and as these drugs are very common drugs and are everyday use of our lives so we have to study them thoroughly starting with aspirin 😊

1) ASPIRIN (Salicylate):

- It is the prototype meaning by that it is the first typical model of NSAIDs as it was first isolated in 1829 from herbs so it is the oldest NSAIDs.
- In the previous lecture we said the structure of aspirin contains Acetyl group and this **acetyl group** binds to Cox1 and Cox2 non-selectively and **irreversibly** because it's a **covalent bond** and this what distinguish it from other NSAIDs that binds reversibly.
- In the previous lecture we said that there are 3 common properties among all of the NSAIDs which are: 1) Anti-inflammatory
  2) Anti-pyretic
  3) Analgesic

Aspirin has a 4th property that doesn't exist in others which is [Anti-platelet] and this property leads us to the 1st application of aspirin.

- **Applications of Aspirin:**

1st application: Anti-platelet

Mechanism: in the previous lecture we said that In the platelets there are vesicles that contain (thromboxane A2 and adenosine) and once the platelets are **activated** they are released from the platelets calling other platelets to come for help and at the end aggregation and clotting of blood so what aspirin does is that it enters the platelets and prevent the production of thromboxane A2 thus decreasing the chance of **thrombosis** (blood clotting) and due to this we use it as a prophylactic for stroke or myocardial infarction and other pathologic conditions that blood clotting have a role In.

This application is mainly done at low dose of aspirin (80mg-100mg) that we call [**baby aspirin**] so baby aspirin doesn't mean that it's for babies , it means

low dose of aspirin and this low dose of aspirin double the coagulation time (time needed for blood to coagulate) compared to people not taking it.

2nd application: Anti-pyretic

Since aspirin binds irreversibly all over the body so it function as **very effective** anti-pyretic drug → decrease the temperature in stronger manner than other drugs because it binds **irreversibly** in the peripheral causing complex events ends with **vasodilation** and this vasodilation is related to [**more sweating**] **= heat dissipation** and the patient will lose the fever very fast and he will be sweating a lot so you can think he got showered!

Note that this effect of aspirin (anti-pyretic) isn't done at low dose of aspirin but **at 325mg or 650mg (2pills).**

***When do we use aspirin as anti-pyretic?**

If the patient is **ADULT** and suffering from something called [**fever febrile]** which is a seizures that happen when there is high temperature (the patient is shivering from temperature) and in this case aspirin is the best choice and we usually give 2 pills in this case .

3rd application: Analgesic

We use (Aspirin + paracetamol + caffeine) to have an **additive** or **synergistic** effect and most commonly additive effect **in treating migraine (moderate to severe pain)**, if you remember what these things mean then good for you, if not read this: [additive effect: 1+1=2], [synergistic effect: 1+1>2] but this application isn't common in our countries, it is mostly used in the USA.

4th application: Anti-inflammatory

Inflammation related to the musculoskeletal such as (Rheumatoid arthritis, osteoarthritis, etc.) the old doctors used to treat them with aspirin which is not a preferred choice for new doctors and please as a new doctor, **SKIP aspirin** because of its severe side effects on the GI tract (every person who took aspirin as anti-inflammatory had a **bleeding in the GI**, even if the bleeding wasn't noticed but it surely happened).

Note that the **dose** for using aspirin as **anti-inflammatory** is : **(975-1200mg) 3 times a day** which means (3-4g) daily and this dose isn't good because when we give aspirin at high dose it becomes a metabolic drug! To know what this means see the next.

***Aspirin as a metabolic drug:**

A metabolic drug is a drug that affects metabolism and aspirin in this case causes uncoupling of oxidative phosphorylation and causing more production of CO_2 thus the patient will **need more oxygen** so you will notice your patient taking deep breathes and this thing is normal and those deep breathes what distinguish this high dose of aspirin (3-4g) daily.

➔ If you give a dose that is higher than (3-4g) daily this will lead to **(intoxication)** and it is remarked by Hyperventilation not deep breathes!

➔ **If a child took aspirin accidently what will happen?**

Uncoupling of oxidative phosphorylation will occur and their body won't be able to response as deep breathes , instead it will response by hyperventilation -> decreased partial pressure of arterial CO_2 thus increase the bicarbonate production and thus increasing PH leading to **respiratory alkalosis** (distribution in acid base balance due to respiratory hyperventilation) and if this process continued the body will try to compensate by trying to secrete the bicarbonate due to their over-production , so the kidney will secrete the bicarbonate but sodium and potassium will be secreted with it so the respiratory alkalosis will turn to **metabolic acidosis.**
Also the body isn't producing the needed energy so it will take the glucose and there will be depletion of glucose causing **hypoglycemia** and all of these effects may lead to death.

How to manage this?
→ Aspirin can be absorbed by **charcoal** so you give it to the patient hoping it will absorb the aspirin but if this didn't work ☹

→ **Gastric lavage** and if this didn't work too ☹ ☹ because aspirin has been absorbed already

→ give him **fluids** and [IV sodium bicarbonate] to produce a urine with a PH > or = 7.5 thus elimination of salicylic acid by the kidneys increased and this increase poison elimination and this process is called (**Alkalization of urine**) SOO It's Contraindicated to give aspirin to children for 2 reasons :

1. They might have **allergy** for it (not common, 1 in 300 patients).

2. **Reye's syndrome**: this is **fatal** and happen if the child had a viral infection and you gave him aspirin, it causes acute liver failure and encephalopathy of the brain.

External applications of aspirin:

1. Giving it not as aspirin but as 20% of Salicylic acid which is a weak acid and we use it to treat warts and foot corn.

2. Prevent cancer although this isn't approved in the world but it's true and it really prevents cancer.

*The most common adverse effect for aspirin is **GI bleeding** because it prevents the prostaglandin activity on the GI so it's a weak acid and have **an irritation activity.**

*Note: if you have a patient that you're going to operate on him, you should ask him if he's taking aspirin because surgeries include bleeding and if the patient is taking aspirin he will have a higher chance of bleeding. If he take aspirin he should stop it 5-7 days prior the surgery due to a thing called (**platelet renewal)** the platelets half-life is 7 days so if he's taking aspirin and it's in his platelets, after 7 days these platelets will die and new ones will be produced which are free of aspirin YAAAY.

The 2nd drug that we are going to talk about is **Acetaminophen = paracetamol**

I'm a drug that sometimes they consider me as a NSAID ^_^ and sometimes they don't ☹ do you know why?

Just because one of the 3 common properties of NSAIDs which is [Anti-inflammatory] is missing in me because I have less effect on cyclooxygenase enzyme in the peripheral tissue. this is not fair ☹ the pharmacy just called and they just told me that I also have a weak Anti-pyretic effect! meaning by that I treat the result weakly (cause a little drop in temperature) but I don't even treat the thing that caused the temperature ! what ? and I also have a weak analgesic effect that is only enough for mild pain and can't be used to moderate pain !!! oh my god ! this means that I share the mechanism with NSAIDs only **centrally** (in brain) by acting on fever and pain and I don't have any effect peripherally ☹ god I feel that I'm useless ☹ why do I exist ☹ what? is that right? oh yay ! guys listen , they told me that I'm the ONLY drug without side effects at the therapeutic dose and that's why I'm common among **children** ! god I

feel so special *_* I don't care if they considered me from NSAIDs or not anymore because all NSAIDs are contraindicated in children below 1 year and among pregnant women but I'm not so I'm the drug of choice during pregnancy and for children below 1 year :$ so I'm a suitable substitute for analgesic / anti-pyretic effects of aspirin for those patients with GI disturbances and those when prolonged bleeding time is disadvantage :$ and I'm the drug of choice for children with viral infection / chickenpox BECAUSE aspirin increase the risk of Reye's syndrome, dieeee aspirin :P

But hey wait, some people think that I'm so peaceful and that they can take me in high doses! no guys you should differentiate between the side effects and intoxication ! 😊 I cause intoxication at: 1) 6-7 g in normal adults.

2) 4-5g in adults who are alcoholic (I'll explain why later).

3) More than 4g in children.

Normally, paracetamol is detoxified by CYPE1 and the final product which is (nucleophile cell micromolecule) is detoxified by Glutathione and excreted from the body, so in the case of intoxication there will be **a depletion of the glutathione** so a toxic material called (NABQI) will accumulate and this causes the death of liver cells **leading to acute liver failure**. The good news is this is not fatal and can be managed by giving the patient *charcoal and gastric lavage*, if didn't work ☹ → give the patient (Acetylcysteine) OR GSH that contain -SH group that will **drain NABQI** so yes I'm a drug without a side effect but **THE SLIDES SAY:** I can cause Hepatotoxicity and Nephrotoxicity when THE DAILY DOSE IS MORE THAN 7.5 g.

Note: 1 tape of paracetamol contains 5g

We said that patients with **alcoholism** (alcohol addicts are called patients) have high induction of CYPE1 so if they take a lot of paracetamol the process will be faster than the liver can deal with and NABQI will accumulate causing intoxication Sooooo

[Avoid chronic and large doses of paracetamol]

Now I'm going to talk about some drugs that you should memorize:

1) Diclofenac, trade name is **Voltaren**, this drug is built up in the synovial fluid once you take it orally so we use it for *musculoskeletal* injuries (such in muscle spasms). **Its half-life is from 1-2 hours** so you give it to the patient **3-4 times a day.**

2) **Ibuprofen**, trade name is (**Advil**), this has 2 applications:

A) Dental application because it builds up under the teeth.

B) Endometriosis and for period pains, because it builds up in the endometrium and its half-life is **2 hours** so you give it to the **patient 3-4 times a day**, the red pill of it is for 200 mg and the green one for 400mg. If it's used as anti-inflammatory, the higher dose must be given to the patient.

3) Naproxen, its half-life is **14 hours** so you give it twice daily.

4) Piroxicam, its half-life is **50 hours** so you give it once daily.

Naproxen and piroxicam are used for **chronic inflammation**. E.g.: gout, arthritis, rheumatoid arthritis and we give them for 1 or 2 months but we should observe the patient due to their side effects.

Finally we are going to talk about a drug that is not commonly used but is considered as NSAID.

Indomethacin or indometacin**: it *inhibits COX1and COX2 like other NSAIDs*, *inhibits phospholipase A & C (like steroids)* and ***inhibits the neutrophils migration and reduce t cell and b cell proliferation so it is a very potent anti-inflammatory.

As the slide says: It is used to juvenile rheumatoid arthritis, gout and ankylosing spondylitis.

But we don't use it commonly because of high incidence of adverse effects that are:

1. GI bleeding (like other NSAIDs) and diarrhea.

2. CNS side effects (mental confusion & frontal headache).

It has been used to treat patent ductusarteriosus, but NOW, it's used as (Ophthalmic preparation) for **conjunctiva inflammation**. Don't be scared *you can use it safely as (mouth rinse)* for **gingival inflammation** but you pay attention NEVER swallow it.

This sheet was written on the honor of: Sadan Ahmed <3

FINALLY THE ENDDDD