

***Title of Lecture: CNS pharmacology***

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***Sheet no: 21***

***Refer to slide no. :9***

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***NOTE: I wrote just the extra things that the dr. said , so u have to refer to slides.***

***Slide 25***

Major mediators for inflammatory reactions: prostaglandins , leukotriens & other enzymes

It's important to know & understand the synthetic machinery of PG & LT , cause this is good in medicine ,it represents possible targets of drugs, not only in inflammation

PG synthesis starts with phospholipids present in our membranes → by phospholipase A2 forming arachidonic acid (a 20 carbon fatty acid) → by cyclooxygenase, prostaglandins are formed ,&by lipoxygenase ,leukotriens are formed .

Let's talk about trauma to the knee for ex.:

 in the beginning, in response to this trauma ,many mediators (PG & LT are 2 of them) will travel to such site to counteract effects of trauma ,

 but later on , it will be swollen , red in color , feeling hot & pain.

Agents that release prostaglandin are highly effective in relieving pain because it have anti-inflammatory effect. So, at the beginning, PGs are good but after a while, they will be response of many manifestations of inflammation . if this inflammatory process is persistent in a body (meaning that PG persist in making irritation) there will be patients with autoimmune diseases as rheumatoid arthritis, vascularitis & other diseases ,they have persistent & continuously inflammatory reaction in their joints & the pain is persistent , the solution for such patients will be to take medications for life (chronic administration) , & this means that there will be side effects as a consequence , or simply we can cut the infected part , so easy ^^ .

Prostaglandins:

They are highly protective for the GI tract -

 - They increase bicarbonate secretion

-they are important for the integrity for the mucous layer that cover the mucosa of stomach, duodenum & the rest of the GI tract

Therefore, inhibition of PG will lead to ulceration & irritation , & both phospholipase A2 inhibitor as well as cyclooxygenase enzyme inhibitor will lead to ulceration because they inhibit PG synthesis .

Anti-inflammatory agents will be classified into :

- non steroidal agents : acts on cyclooxygenase

-Steroidal agents : acts on phospholipase A2

Both will inhibit PG synthesis.

Leukotriens

with respect to LT , we notice that a number of LT (B4, C4, D4) are known as Slow Reactive substance of anaphylaxis (SRS-A) (it’s the substance that is responsible for the severe bronco constriction that occur in patients with bronchial asthma or anaphylaxis ), so , LT is responsible for bronco constriction . so ,drugs that inhibit the LT will be useful in the treatment of bronchial asthma & hypersensitivity rxns.

NOTE:

- both LT & PG are incorporated in inflammatory rxn

 Some of PG are good for the contraction of uterus-

Most of PGs are protective for the GIT-

 -Some of PG are good bronchodilators & some others are good bronchoconstrictors

- prostacyclin (PGI2) is a good platelet aggregation inhibitor & a good vasodilators

-thromboxins (TXA2) produces vasoconstriction.

-in cases of inflammation , PG & LT must be inhibited cause they are harmful in such a case, this is accomplished by using specific antagonist (but we don’t have antagonist) cause we believe that their effects are receptor mediator, we don’t have many available antagonists cause NSAIDs are highly effective in management of inflammatory rxns

A useful PG is synthesized by main analogs, ex. Those which contract the uterus (good contractors) synthesized from some of the agonist PGE group or PGF2 alpha they are good in delayed delivery, no contraction at the time of delivery in uterus ,so such PG are available in vaginal dosage forms , oral dosage or parentral dosage form.

Synthetic analog is effective in cases of :

1.GIT

2.peptic ulcer(specially answers induced by drugs , steroidal or none steroidal.

Note: we can make agonists but we can't make antagonists, cause there is no need for them ,inhibitors are highly effective and very safe . Actually there is a little bit antagonists, but the wildly used are in inhibitors.

NSAIDs:

Contra indication:

1. We don’t use it with patient having peptic ulcer

2. There will be left shift: when you inhibit cyclooxygenase, there will be a left shift in the synthetic machinery towards LT, so NSAIDs are absolutely contra indicated with patients in bronchial asthma.

Note:

-LT produces bronchoconstriction

-Steroids are not contra indicated with bronchial asthma, especially in steroidal dependent bronchial asthma ,but NSAIDs absolute contra indicated with bronchial asthma .

We have 2 PG that have action on platelets and the diameter of blood vessels: TX & PGI2

|  |  |
| --- | --- |
| prostacyclin(PGI2)  | thromboxane |
| -it formed in blood vessels cause It contain prostacyclin synthase enzyme.-it’s a good vasodilator and inhibitor for platelet aggregation. -synthetic machinery from the beginning : phospholipase A2 in blood vessels 🡪 arachidonic acid 🡪 prostacyclin synthase enzyme . | -formed in platelets cause it contain Thromboxane synthase enzyme.-it’s a good vasoconstrictor and increase platelets aggregation. –synthetic machinery from the beginning: phospholipase A2 in platelets🡪 arachidonic acid 🡪cyclooxygenase in platelets 🡪 thromboxane synthase enzyme. |

Both TX and PGI2 work in balance, one is vasoconstrictor and other is vasodilator.

If the blood is liquefied, then prostacyclin is working more, but if the blood is coagulated, then TX is working more, they act in balance.

Ischemic heart disease starts with irritation in coronary arteries, there is damage that is resulted from smoking or deposition of lipids in blood vessels🡪when damage occur in early phase of healing there will be very quick migration of platelets toward site of injury (agglutination) forming clot 🡪 lipid will deposit around and enclose the damage. In early phase its preferred to have vasodilation to enlarge the area but when there is vasoconstriction it will close more so TX is harmful in this case and we prefer PG to work.

(We need TX in patients with ischemic heart disease)

How to make PG works?

We use an analog, or just inhibit TX by TX inhibitors and these are wildly used to inhibit hypertension so we inhibit a vasoconstrictor (LT) to have an action of PG to do vasodilatation.

What do you know about aspirin? How it acts?

-it’s a liquefied agent for blood.

It's an NSAID (but have transient antiplatelet action)

(Note: in cases of bleeding, we care about platelets activity more than vasodilatation).

-Aspirin (but not other NSAIDs) reversibly inhibits vascular cyclooxygenase, but irreversibly platelets cyclooxygenase, this is the mechanism of antiplatelets activity of aspirin.

Clarification :

When you take one tablet of aspirin, all the cyclooxygenase present in platelets will be inhibited irreversibly so there will be no TX, in order to have TX in platelets a new cyclooxygenase is needed that present in a new platelets , and the new platelets are formed by the bone marrow every 14 days ,so these platelets will have new cyclooxygenase and could make know a new TX ,so the aspirin will inhibit TX for 14 days but on the other hand PGI2 will be inhibited just for 3 hours (reversibly inhibited).

To inhibit TX for ever just take an aspirin every day in low dose , by this you will inhibit TX formation permanently and allowing formation of PGI2.

This represents the good activity of aspirin on platelet and insure the saying :

One tablet of aspirin a day could protect against myocardial infarction after the age 15.

-some studies says that taking one tablet every other day (300mg) is better than taking it daily (80 mg) ; cause the harmful effects will be less.

-NOTE: other NSAIDs rather than aspirin will inhibit reversibly both: platelet & vascular cyclooxygenase equally.

***Slide 26 & 27*** … nothing extra

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-selective NSAIDs : acts on COX2 only that inhibits PG in all tissues except kidney , platelet & stomach , it will have anti-inflammatory effect but it won't be that harmful to stone kidney patients , & could be used also in patients with peptic ulcer as analgesic . remember that selectivity is not 100%.

NOTE

-that there is a great individual variation between NSAIDs in response & tolerance for the side effects. Some patients for ex. if take a certain NSAIDs will have vomiting , in this case the patient could use another drug, or if it’s a problem in the non selective , try to use the selective one cause its effect on the GIT is better.

- The non selective inhibitors have less effect on platelets & kidney especially with patients having hypertension, NSAIDs usually elevates blood pressure, but the non selective is a little bit better.

-selective COX2 inhibiters : patients are protected against colonal cancer , also has effect on fertility or as contraceptive.

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-Dazoxiben & Hydralazine ( TX synthase inhibiters) are effective in the management of hypertension.

-Zileuton ( lipoxygenase inhibitor) & Zafirlucast (leukotriene antagonist) are used with patients having bronchial asthma . both are highly effective orally & not used in large doses. notice that these 2 drugs are not effective in the treatment of peptic ulcer , cause the shift in this case is not good enough but they are good in producing bronchodilatation.

-what happens when LT formation is inhibited by NSAIDs?

There will be a right shift , & this is good in cases of peptic ulcers.

-the drug that inhibit lipoxygenase & make reasonable right shift for peptic ulcer disease should be in a large dose & this means side effects.

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-disease modifying antirheumatic drugs :

Such drugs usually hit the defect itself rather than inhibiting PG & LT in an attempt to cure rheumatoid arthritis ,but these drugs are not highly effective in treating this disease or other autoimmune disease.

-Acetaminophen = paracetamol = panadol :

Has no anti-inflammatory effect , but has a good analgesic & antipyretic activity . has no effect on peripheral PG synthesis but inhibits PG synthesized centrally.. its not contraindicated with patients having bronchial asthma, reye's syndrome or peptic ulcer . analgesic & antibiotic effect of paracetamol is mainly due to

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GOUT:

 its high uric acid in blood , starts with inflammation to the joints. When there is deposition of uric acid in joints, there will be an inflammatory rxn that is responsible for acute attack of gout that could be solved by the administration of one of the NSAIDs ,cholchicine a drug of choice anti-inflammatory agents, but later on with running cases (chronic) we have to increase excretion of uric acid or to inhibit synthesis by allopurinol

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inflammation of NSAIDs involves many enzymes of coagulation system, complement system & many mediators ,PGs & LTs are major mediators. Such drugs inhibit PG synthesis by inhibiting cyclooxygenase wether it is selective or non selective ,they have a good anti-inflammatory rxn.

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(All should be memorized)

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-diclofenac: is a widely used anti-inflammatory NSAIDs drug. its highly effective in

1- renal colic (pain that results from stone) orally & parentraly.

2- has some dilating effect on ureter

-voltaren …available as such diclofenac, there is diclofenac sodium & diclofenac potassium that are used in specific cases. Using Meclofenamate alone is better cause it has no effect with sodium , potassium or others. Voltaren is a very useful drug.

NOTE: NSAIDs have anti-inflammatory but not antibacterial activity , so they relieve the pain due to inflammation . bacterial infection could be accompanied with inflammation & its treated by antibiotics ,chemotherapeutic agents ….etc

-Ibuprofen: a lot of ladies take it cause it considers the best in dysmenorrheal .its an excellent drug.

-naproxen: dentists like prescribing this drug . (NAPROXEN…NO PAIN). It’s a Jordanian drug.

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There are individual variations with different NSAIDs in respect with their efficacy as well as to their tolerance to side effects, so if a patient has a side effect by one of the NSAIDs, he or she can use another one cause not all NSAIDs will produce the same severity.

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-patency of ductus arteriosus :

ducts (duct that connects pulmonary artery with aorta) that are kept open by PG during fetal life. During fetal life, blood doesn’t go to the lung , instead it goes to aorta directly cause there is no need to go to the lung (there is no breathing) during this period. After delivery this duct will be closed, so blood will goes from right ventricle to lungs .suppose that u have a baby that is delivered patent ductus arteriosus ( open duct after delivery) , then it has to be closed by inhibition of PG.(Indomethacin) is highly effective in closing as such duct. Sometimes we have to keep this duct open after delivery & this could be accomplished by giving PGE analog (ultrastatin) .

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NSAIDs side effects :

1. PG synthesis inhibition related

( some effects are related to inhibition of PG synthesis & others are not related)

-PG synthesis inhibition affects the GIT in cases of ulceration , bleeding,…etc.

-prolonged bleeding time

- Delayed parturition … PG that contracts the uterus is inhibited.

-allergic reaction ... bronchospasm for example due to left shift.

 - renal effects … they lead to retain Na+ , so elevating pressure –

 hyperkalemia – renal failure.

* Its not absolute contraindicated , but be careful when using NSAIDs with bronchial asthma , peptic ulcer or hypertension cases.
1. PG synthesis inhibition unrelated :

-hepatotoxicity : unique side effect for NSAIDs not related to PG

-CNS effects

(hepatotoxicity & the CNS effects are the most obvious effects for the unrelated inhibition)

-nephropathy : there are certain side effects on the kidney not related to PG like ;renal papillary necrosis , acute interstitial nephritis, acute renal failure .

NOTE: potentiation …the combined analgesic therapy could be harmful to the kidney to the extent that there is what is known as analgesic nephropathy.

***Slide 45*** … not recommended

***Slide 39 & 40***

Aspirin

-in the past aspirin was widely used with children & to commit suicide.

- its an analgesic, antiplatelet, anti-inflammatory & antipyretic drug.

Aspirin clinical uses:

-antiplatelet function to protect against MI (in low dose)

-intermediate dose is required for mild to moderate pain like headache .

-a larger dose is required for rheumatoid arthritis.

- the largest dose for rheumatoid fever that occur due to problems with valves & joints following tonsillitis by beta hemolytic streptococci , meaning that if tonsillitis is not cured , this may lead to rheumatic fever.

Aspirin side effects :

-gastric irritation

-bleeding (due to aspirin's antiplatelet activity)

-brochoconstriction … not due left shift only, but patients with bronchial asthma are more sensitive aspirin unlike other NSAIDs)

-toxic effect : salicylism ( it’s a syndrome that is characterized by dizziness , tinnitus, nausea & vomiting).

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Aspirin contraindication :

* Peptic ulcer
* Bronchial asthma
* Reyes' syndrome : its contraindicated to use aspirin in children having common cold cause as noticed this lead to death ,& the died children had have brain & kidney damage.

\*Buffered aspirin :is an aspirin with an antacid & its contraindicated with patients having peptic ulcer.