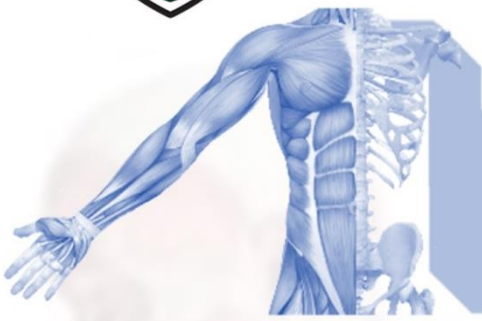


MSS

Musculoskeletal System

Doctor 2019 | Medicine | JU

5 Pharmacology

Writer: Sohib Al-shabatat

Scientific correction: Sohib Al-shabatat

Grammatical correction: Sohib Al-shabatat

Doctor: Alia Shatanawi

Analgesics

Analgesics are medication that are used to suppress the pain.

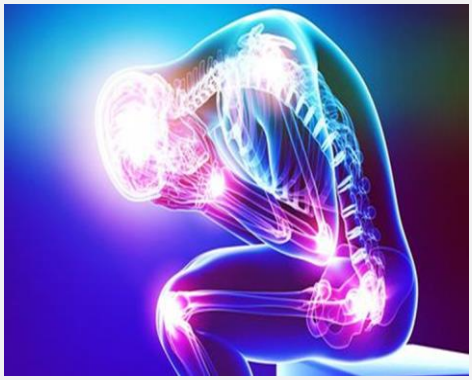
Derived from Greek **an**- "without" & -**algia** "pain".

= An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain.

Drugs that relieve pain **selectively** without blocking the conduction of nerve impulses, they **don't** alter sensory perception or affect the consciousness (this is the difference between analgesics and anaesthesia).

these drugs act in various ways on the peripheral and/or central nervous systems.

Pain



Pain is unpleasant sensation that can either be acute or chronic, usually related to some type of tissue damage and serves as a warning signal.

No. 1 Reason people take medications.

The drugs that work on central nervous system are called Narcotic (or opioids), on the other hand Non-Narcotic drugs (nonopioids) belong to a group of drugs called non-steroidal anti-inflammatory drugs (NSAIDs).

The difference is illustrated in the table in the next page…

Comparison of Analgesics

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid) (NSAIDs)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central nervous system	Peripheral and Central "Mainly peripheral"
Mechanism	Specific Receptors Opioid receptor	PG Synthesis (prostaglandin)
Danger Side effects	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic خافض حرارة	No	Yes
Antiplatelets مضاد تخثر	No	Yes

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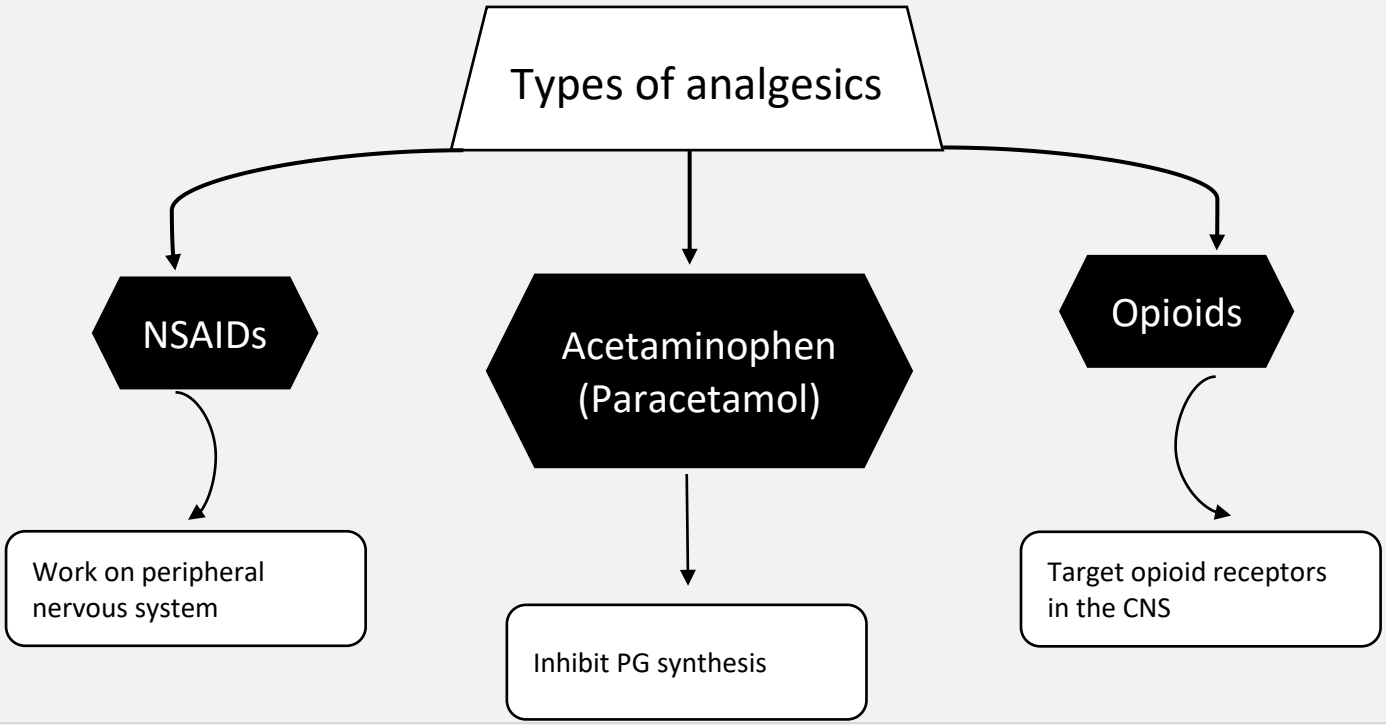


NSAIDs

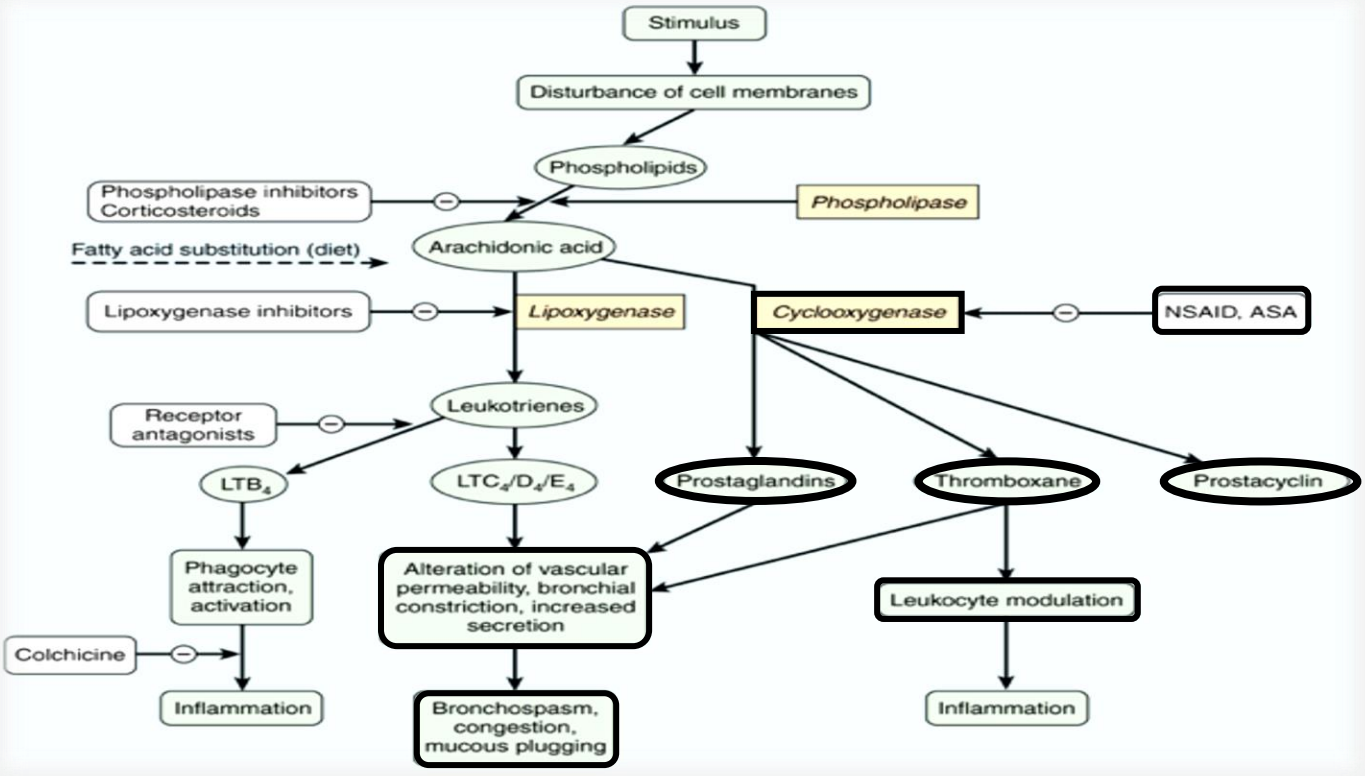
The NSAIDs are a group of chemically dissimilar agents that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

Mechanism of action: <u>inhibiting</u> the **cyclooxygenase** enzymes that catalyse the first step in prostanoid (PG) biosynthesis.

Remember

Cyclooxygenase is part of arachidonic acid metabolism which produces PG, so NSAIDs will decrease PG synthesis with both beneficial and unwanted effects.

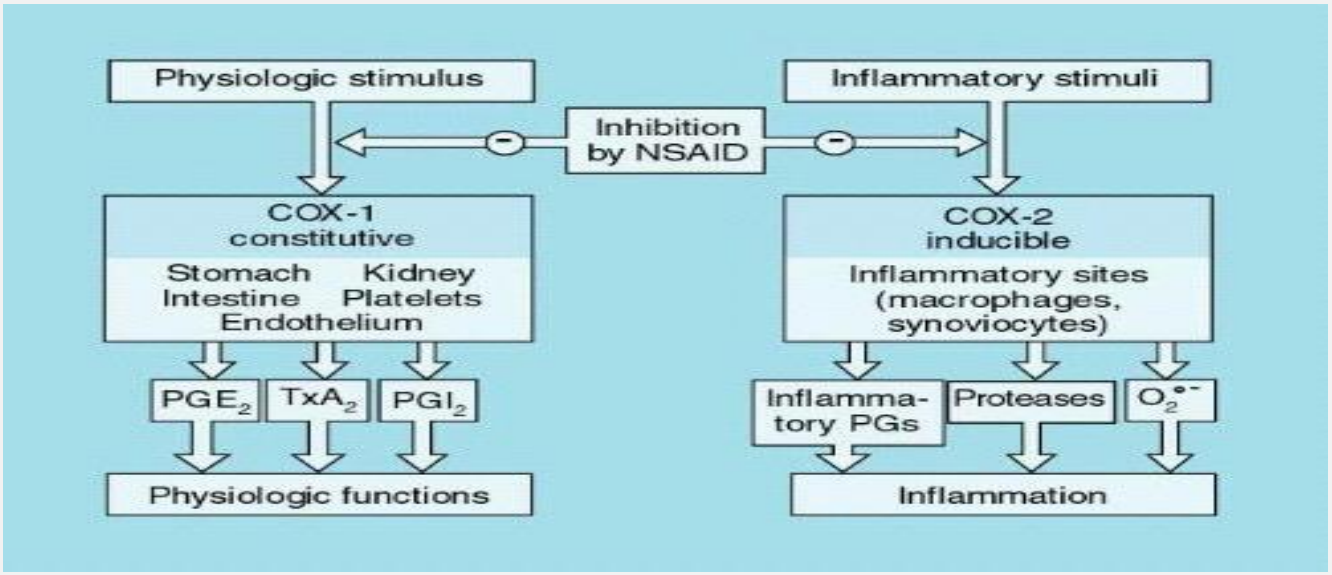
Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins which has effects on blood vessels, on nerve endings, and on cells involved in inflammation.



Remember that we have 2 types of cyclooxygenase enzyme:
-cyclooxygenase 1 which exist in the tissue as constitutive form (physiological response).
-cyclooxygenase 2 the inducible form which found in the site of inflammation.

>>inhibiting these enzymes will inhibit the production of their products which are PG (for both) & prostacyclin and thromboxane (for COX-1).

when we inhibit these PGs we not only inhibit the inflammation but also we will lose important function that they do..
Ex: in the stomach PG-E_2 protect the stomach from the excessive acid secretion (it increases the mucus production and lower the acid secretion from parietal cells), so inhibiting PG-E_2 will lead to over secretion of HCl and lower the protection of mucus layer and because of that these drugs cause GI irritation.



inhibiting COX-2 specifically will inhibit the inflammation without affecting the physiological functions of COX-1…

members of NSAIDs are selective for COX-1..we are trying to develop COX-2 selective drugs…

NSAIDs anti-inflammatory effect

1} decrease Vasodilator PG (PGE2, PGI2) leads to less vasodilatation and, indirectly, less edema.

2}The inhibition of activity of adhesion molecule (that help of transferring inflammatory cells from the blood to the site of inf. (cadherins & selectins))

Remember Immuno

3} Accumulation of inflammatory cells is also reduced (due to point 2).

NSAIDs analgesics effect

1] Decreased prostaglandin generation means decrease sensitivity of **nociceptive** nerve endings to inflammatory mediators.

يعني كأنه ال PG بشغل هذا الريسيبتور

2] Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation in the head.

From google

Nociceptors are sensory receptors that detect signals from damaged tissue or the threat of damage and indirectly also respond to chemicals released from the damaged tissue.

NSAIDs antipyretic effect

this is partly due to a decrease in the mediator prostaglandin that is responsible for elevating the hypothalamic set-point for temperature control in fever.

Aspirin:

One important member of NSAIDs family, actually it's the prototype of this family that can cause **irreversible** inactivation of COX-1 and COX-2.

-it was approved by FDA in 1939

**its modified natural source come from acetyl salicylic acid which is constituent of bark of Willow tree لحاء شجر الصفصاف

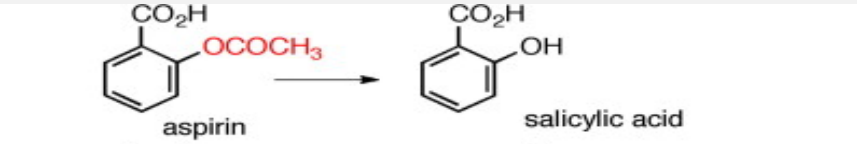
*It is the **most** commonly used and is the drug to which all other anti-inflammatory agents are compared to it..

Acetylsalicylic acid

Mechanism of action:

Aspirin is a weak organic acid that is unique among the NSAIDs in that it **Irreversibly** inactivates cyclooxygenase while the other NSAIDs are all reversible.

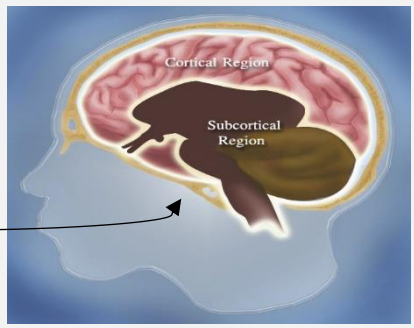
- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.



The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centres in the hypothalamus and at peripheral target sites.

Furthermore, by decreasing **prostaglandin** synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli.

** Aspirin may also depress pain stimuli at **subcortical** sites.



Aspirin analgesics effect

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process, by this we desensitize the nerve ending and thus decrease the pain sensation.

=So, it's used to management of low and moderate pain intensity specially that arise from musculoskeletal disorders (muscle, bone, headache) than the visceral pain (where we use opioids).

Aspirin antipyretic effect

Fever occurs when the set-point of the anterior hypothalamic thermoregulatory centre is elevated.

*impeding PGE2 synthesis and release > resets the hypothalamus toward normal.
** it rapidly lowers 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 يعني ما بنزل الحرارة لأقل من الطبيعي لانو وظيفته يعيد ضبط ال Hypothalamus.

Respiratory action of aspirin

-At therapeutic doses, aspirin increases alveolar ventilation causing uncoupling of oxidative phosphorylation, which leads to elevated CO2 and increased respiration.

-Higher doses work directly on the respiratory centre in the medulla of the brain, resulting in hyperventilation and respiratory alkalosis.

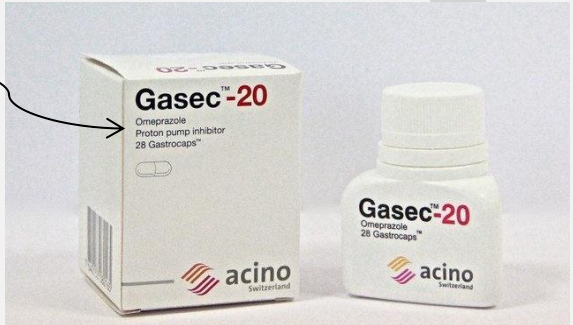
-At toxic levels, it cause central respiratory paralysis which leads to acidosis.

Gastro-intestinal effect of aspirin

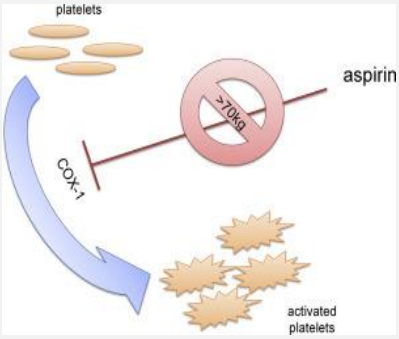
-Remember, PGE2 stimulate synthesis of protective mucus in both the stomach and small intestine.

-In the presence of aspirin, these prostanoids (PG) are not formed, resulting in increased gastric acid secretion and diminished mucus protection.

-People who have to use aspirin will have problem with increase acid secretion, to solve the problem we give them proton pump inhibitors (PPI) these drugs inhibits the gastric and duodenal ulcers (for example of PPI: esomeprazole, lansoprazole, omeprazole.



Aspirin effect on platelets



-Remember that cyclooxygenase pathway produces thromboxane (TXA_2) which enhances platelet aggregation, so low doses 81 mg daily of aspirin can irreversibly inhibit thromboxane production in platelets.

Usually for irreversibly acting drugs the action stops after the body produces the enzyme that was inhibited,, now note that platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (7 days)>> As a result prolonged bleeding time, so be careful about that.

Aspirin action on kednys

-Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 (prostacyclin) that are responsible for maintaining renal blood flow, so some people will have kidney injury because of the decrease in renal blood flow.

-Additionally, decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalaemia in some patients.

=note that, **Interstitial nephritis** can also occur with all NSAIDs except aspirin.

Therapeutic uses of aspirin

Anti-inflammatory, antipyretic, and analgesic uses:

-The salicylic acid derivatives are used in the treatment of gout النقرس, rheumatic fever, osteoarthritis, and rheumatoid arthritis.

=Commonly treated conditions requiring **analgesia** include headache, arthralgia ألم المفاصل , and myalgia ألم العضلات.

*any kind of pain related to musculoskeletal system.

External applications:

-Salicylic acid is used topically to treat corns مسمار اللحم and warts الثآليل because it has keratolytic activity.

Cardiovascular applications:

-Aspirin is used to inhibit platelet aggregation, low doses are used **prophylactically** to:

1. reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death. Patient who have history of CV diseases or hypertension or even elderly patient who have diabetes are prescribed aspirin to protect the CVS from ischemic attacks or thrombotic events.
2. reduce the risk of death in those having an acute **myocardial infarction or angina.**

Pharmacokinetics of aspirin

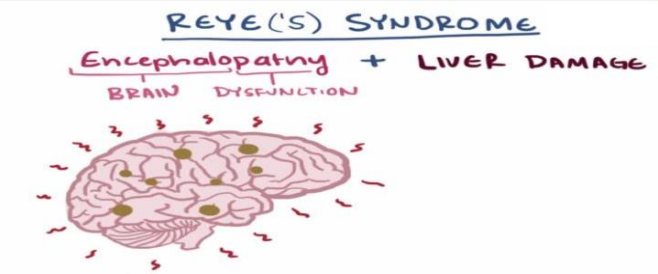
Administration and distribution:

-After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine.**

-it can be given as suppository تحاميل, so we have **Rectal** absorption of the salicylates which is slow and unreliable, but it is a useful route for administration to vomiting children.

=important: Salicylates must be avoided in children and teenagers (<15 years old or <12 sometimes) with varicella (chickenpox) or influenza, because the use of salicylates is associated with a syndrome called **Reye's** syndrome which can be fatal.

-so in children we use paracetamol which is one of the safest drugs to use.



Dosage:

الأرقام مش حفظ

-in aspirin we need high doses to reach the anti-inflammatory effect while we need low dose to reach the analgesic or platelet effect.
-Ex: 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.
-Ex: For long-term **myocardial infarction prophylaxis**, the dose is 81 to 162 mg/day.

Fate:

الدكتورة ما قرأتهم بس موجودين بالسلايدات

-At dosages of 650 mg/day, aspirin is hydrolysed 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.
=aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

Adverse effects

Gastrointestinal:

The most common GI effects of the salicylates are **epigastric distress**, nausea, vomiting and microscopic **GI bleeding.**
=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.

Blood:

-inhibition of **platelet** aggregation and a prolonged bleeding time (1 week).

Respiration:

-In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic **acidosis**.

Metabolic processes:

-Large doses of salicylates **uncouple oxidative phosphorylation**. The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the **hyperthermia** caused by salicylates when taken in toxic quantities.

Hypersensitivity: approximately 15% of patients taking aspirin experience hypersensitivity reactions.

=Symptoms of true allergy include urticaria, bronchoconstriction, or Angioedema,,Fatal anaphylactic shock is rare.

Reye's syndrome:

-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.

This is especially encountered in children, who therefore should be given acetaminophen (paracetamol) instead of aspirin.

Drug interactions

Salicylate is 90-95% plasma 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** (anti-coagulant), **phenytoin** (anti-epileptic) or **valproic** acid (anti-epileptic), resulting in higher free concentrations of the other agent.

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

عشان تفهم شو يعني روح عالجدول ص13

In pregnancy:-

-Aspirin is classified by FDA as pregnancy category C risk during Trimesters 1 and 2.

-category D during Trimester 3.

in women who has experienced miscarriage الإجهاض because of the rejection of the fetus because of the formation of antibodies against him, sometimes we encourage them to use aspirin in low doses in the first trimester to increase the circulation to the fetus.

Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breastfeeding.

Toxicity

*** The mild form is called salicylism.**

**seen as nausea, vomiting, marked hyperventilation سرعة تنفس, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).

In serious cases, mandatory measures include the intravenous administration of **fluid**, **dialysis** (تنقية الدم عند عدم عمل الكلى) to correct the **acid-base** and electrolyte balances.

= Ingestion of as little as 10 g of *aspirin* can cause death in children.

Propionic acid derivatives:

They are NSAIDs other than aspirin.

Examples are:

Ibuprofen, naproxen, fenoprofen, ketoprofen , flurbiprofen

These drugs are reversible inhibitors of the cyclooxygenases, so they possess anti-inflammatory, analgesic, and antipyretic activity.

- their GI effects are generally less intense than those of aspirin.

All are well absorbed on oral administration and are almost totally bound to serum albumin.

They undergo **hepatic** metabolism and are excreted by the **kidney**.

The most common adverse effects are **GI** irritation, ranging from dyspepsia سوء الهضم to bleeding.

=Side effects involving the central nervous system (**CNS**) are headache, tinnitus طنين الأذن, and dizziness.

-ibuprofen and naproxen:

=are category C and D risk on pregnant women from the 3rd trimester.

=Increase the risk of cardiovascular thrombotic event, MI and stroke.

=Increase risk of GI bleeding.

=Ibuprofen mustn't exceed 3200mg/day., and taken with food or with water to avoid GI irritation.

its contraindicated or given with caution to asthmatic patient,, because when we inhibit the synthesis of PG, more leukotriene will be produced, remember that they cause bronchoconstriction and increase bronchial secretions.

FDA Pregnancy Categories

الجدول من النت ومش مطلوب بس
عشان نفهم مستويات الخطورة عالحمل

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

Acetic acid derivatives:

Ex: indomethacin, sulindac, Etodolac.

** These drugs are cyclooxygenases inhibitors, so they possess anti-inflammatory, analgesic, and antipyretic activity.

Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis and ankylosing spondylitis التهاب الفقرات التصلبي.

* 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.

Oxicam derivatives:

Ex: Piroxicam and **meloxicam.**

*used to treat rheumatoid arthritis(RA), ankylosing spondylitis, and osteoarthritis.

*They have **long half-lives**, which permit once-daily administration, and the parent drug and its metabolites are renally excreted in the urine.

***Meloxicam** inhibits both COX-1 and COX-2, with preferential binding for COX-2 so it's considered somewhat selective for COX-2 , and at low to moderate doses shows less GI irritation than piroxicam and other NSAIDs.

Fenamates:

Ex: Mefenamic acid.

they have no advantages over other NSAIDs as anti-inflammatory agents, they share the same mechanism of action & the same effects.

Their side effects, such as diarrhea, which can be severe, and they are associated with inflammation of the bowel.

*Cases of haemolytic anaemia have been associated with these agents.

Heteroaryl acetic acids:

Ex: Diclofenac and tolmetin, ketorolac.

*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 so its used in the inflammatory conditions of the joints.

*and the primary route of excretion for the drug and its metabolites is the kidney.

Extra info: voltaren= diclofenac

Diclofenac sodium:

Used orally 50mg after food, I.M. injection 75mg.

*Diclofenac potassium is prompt release بينتشر أسرع and has quicker onset whereas the Diclofenac sodium is delayed release.

*category C risk in pregnancy & its toxicity is similar to others.

*it can cause hypersensitivity.

contraindicated in asthmatic patients & patient with history of peptic ulcer قرحة هضمية

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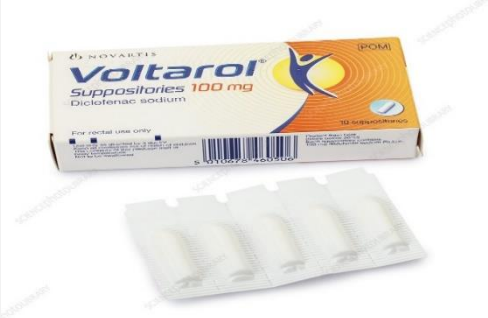
* Metabolism: liver / excretion: urine.



Selective COX-2 inhibitor:

Ex: **Celecoxib, Meloxicam and Rofecoxib.**

*they are new drugs, approved around the year 2000, more selective for COX-2 than for COX-1, synthesized to avoid the GI side effects of non-selective COX inhibitors.

* Rofecoxib actually withdrawn from the markets because it was associated with deaths related to thromboembolic effects, while celecoxib is still available and is used in chronic inflammatory conditions such as RA.

**side effects: its also associated with thromboembolic effects, because remember when we inhibit one arm of the reaction the other arm will exaggerate so inhibiting COX-2 will over stimulate COX-1 which produce thromboxane that cause platelet aggregation.

because of that celecoxib has black box warning says that you have to be careful if you are prone to thromboembolic events so it should be sold with doctor prescription and not OTC (over the counter).

Black box warning is a very serious side effect that have to be written on the outside of drug box.

Acetaminophen (Paracetamol):

Acetaminophen inhibits prostaglandin synthesis in the CNS This explains its antipyretic and analgesic properties but it doesn't have so much anti-inflammatory property.

**it has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity.

**it also does not affect platelet function or increase blood clotting time.

Extra info:
Paracetamol is
The trade name

Therapeutic effect

Acetaminophen is a suitable **substitute** for the analgesic and antipyretic effects of aspirin for those patients with **gastric** complaints, those in whom prolongation of **bleeding** time would be a disadvantage يعني الناس الي ما لازم يكون دمهم مائع ف بنستعمل باراسيتامول بدل الاسبرين, or those who don't require the anti-inflammatory action of aspirin.

**Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that aspirin increases the risk of Reye's syndrome).

Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract, a significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes.

Under normal circumstances, acetaminophen is conjugated in the liver to form inactive metabolites, a portion of acetaminophen is hydroxylated to form N-acetylbenzoiminoquinone which is a highly reactive and potentially dangerous metabolite.

At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance but when we take too much of acetaminophen this can lead to accumulation of the toxic metabolite, so it's important to monitor the dose of acetaminophen.

**acetaminophen is safe drug but if given in high doses it shows toxicity.
=the dose available in pharmacies is 500mg we always take about one to two tablets for headache or other pain every 6h and it's the recommended dose, the safe dose is to take up to 4g (8 tablets), patients who have chronic pain may take more than that which cause the toxicity due to accumulation of the metabolite in the liver.

**Acetaminophen and its metabolites are excreted in the urine.

Adverse effects

-With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects.

-Renal tubular necrosis and hypoglycaemic coma are **very rare** complications of prolonged, large-dose therapy.

large doses can cause Hepatic necrosis, a very serious and potentially life-threatening condition, we treat it by **acetylcysteine** which will remove these toxic radicals, its benefit if given before 8hs up to 12hs of the overdose of acetaminophen, after that we start to see pathology or necrosis of the liver.

*Renal tubular necrosis may also occur.

*Periodic monitoring of liver enzymes tests is recommended for those on high dose acetaminophen.

يعطيكم ألف ألف عافية