



Artery Academy

Done by Mariam Yacoub

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

&

Acetaminophen

Pharmacology II

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اليوم ح نكمل تفريغ الشابتري ان شاء الله

بس إنه ما ح نخط صور أدوية بهاد الفايل بناءً على طلبكم 🙏

Salicylic acid derivatives

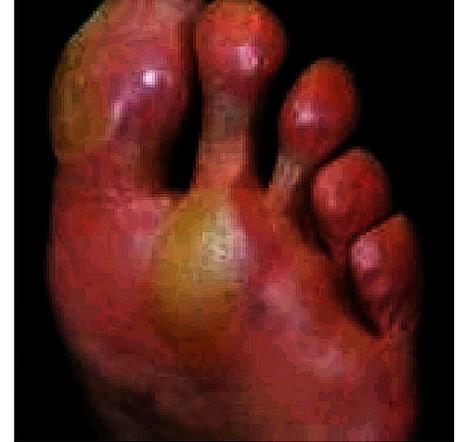
أول category ح نحكي عنها بال NSAIDs هي ال salicylic acid derivative مثل :

- Example: aspirin, salicylate salts and diflunisal
- Salicylates (with the exception of aspirin) are reversible nonselective inhibitor of cyclooxygenase.

كل مشتقات ال Salicylic acid ما عدا الأسبرين يُعتبروا **non selective COX2 inhibitor**
Therapeutic uses:

يُستخدم في علاج :

- External applications: Salicylic acid is used topically to treat acne, corns and calluses (painful thickenings that form in the skin in areas of excessive pressure. A callus refers to a more diffuse, flattened area of thick skin, while a corn is a thick, localized area that usually has a conical or circular shape.) and warts (local growth in skin). **تواليل warts**
- Methyl salicylate ("oil of wintergreen") is used externally as a cutaneous counterirritant.



counter irritant يعني وقت ينحط على الجلد بعطي شعور مثل برودة او حرارة بتروّح شعور الألم

طبعا ال calluses هو بشيه مسامير اللحم corns بس يكون على مساحة أكبر وبالأماكن إلي عليها ضغط الجسم "أسفل القدم" شوفوا الصور عاليمين الأولى calluses والثانية تحت corns

Salicylic acid derivatives

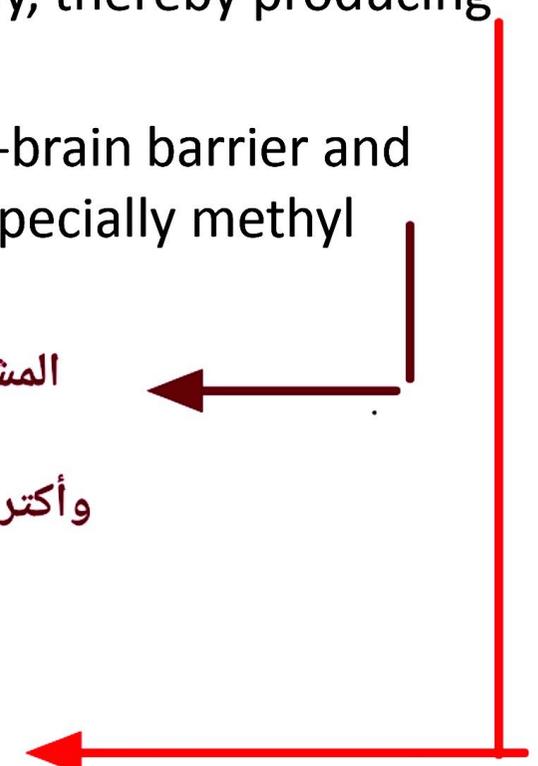
Pharmacokinetics: Orally Available

- After oral administration, the un-ionized salicylates are passively absorbed partly from the stomach and mostly from the upper small intestine.
- Aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate.
- Salicylates (except for diflunisal) cross both the blood-brain barrier and the placenta and are absorbed through intact skin (especially methyl salicylate).

Salicylate ---> except diflunisal ----> cross : BBB and placenta المشيمة
and intact skin الجلد السليم

methyl salicylate هو intact skin ال خلال من عالي امتصاصه

Acetylsalicylic acid (Aspirin) $\xrightarrow[\text{By esterase}]{\text{Deacetylation}}$ Salicylate

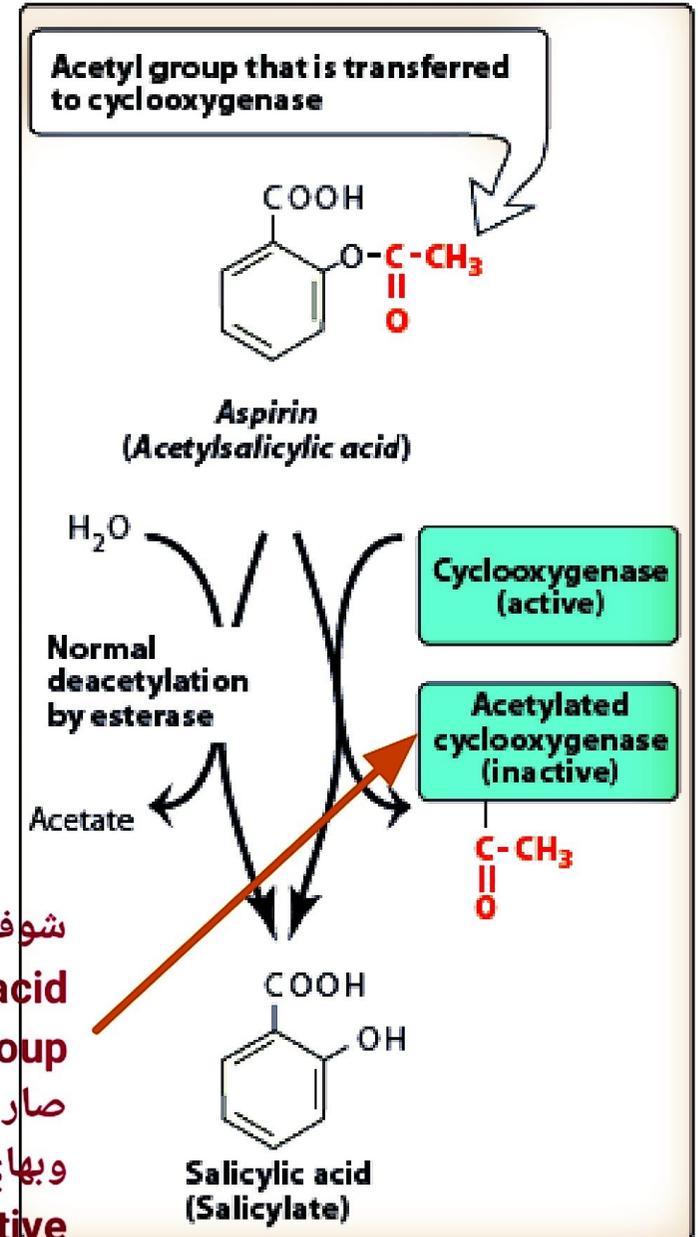
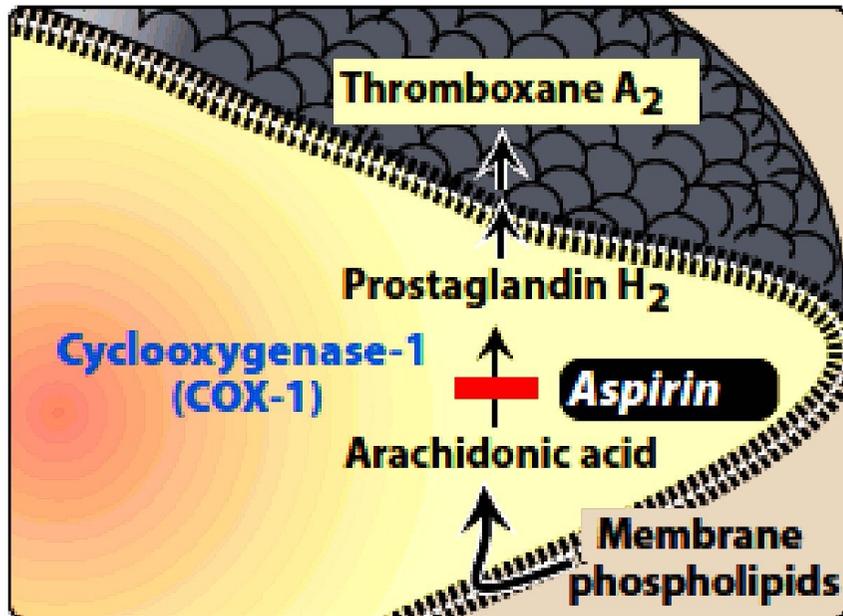


كيف بشتغل الأسبرين ك مميع ؟ عن طريق ميزة خاصة فيه إنه بيعمل **inhibits platelet COX** ف بالتالي ال **platelet** ما حتقدر تصنع انزيئات جديدة ، وهالشي ح يكون **irreversible** ف نتيجة عنه ح يستمر تأثير ال **antiplatelet** من ٨ لعشر أيام

Aspirin

Mechanism of action:

- Aspirin irreversibly inhibits platelet COX so that aspirin's antiplatelet effect lasts 8–10 days (the life of the platelet). **ب other tissue بتشكل COX جديد بدل ال in active COX**
- In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a **duration of action of 6–12 hours.**



شوفوا بالصورة كيف ال **Salicylic acid** أعطى ال **acetyl group** ل **COX** ف صار **acetylated COX** وبهاي الحالة ح يكون **inactive**

Aspirin

have antiplatelet effect

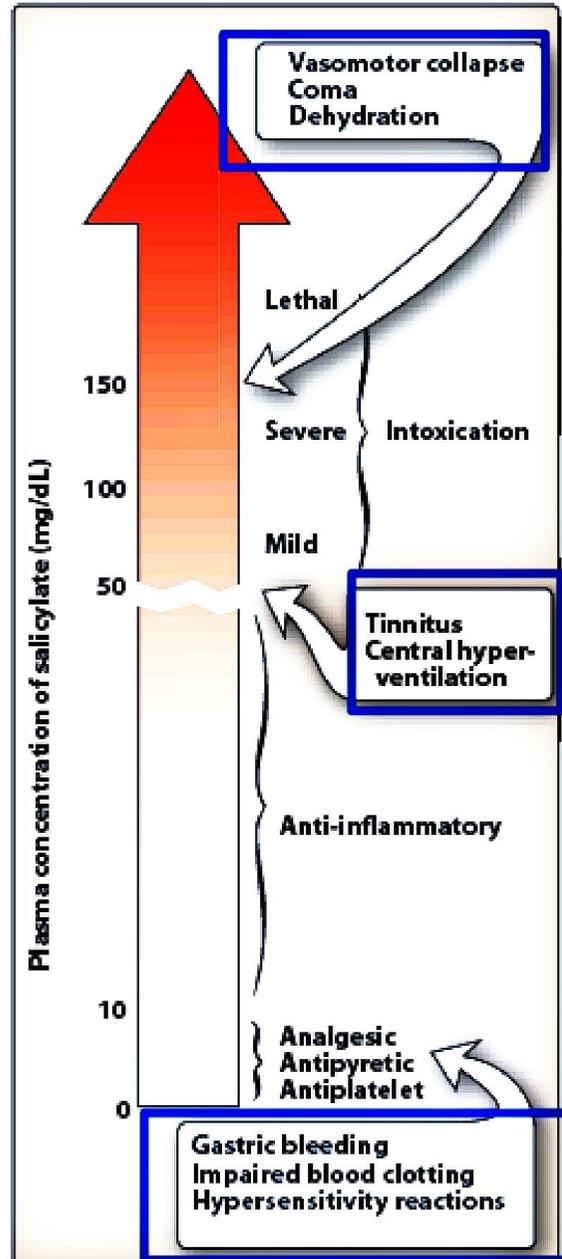
irreversible inhibits for COX in platelet

شوفوا كيف تأثير الأسبرين ممكن
يختلف حسب اختلاف ال dose

- Aspirin has 3 therapeutic dose ranges:
 - The low range (<300 mg/d) is effective in reducing platelet aggregation. anti platelet
 - intermediate doses (300–2400 mg/d) have antipyretic and analgesic effects. مسكن وخافض للحرارة
 - high doses (2400–4000 mg/d) are used for an anti-inflammatory effect. anti inflammatory
- In the presence of other NSAIDs, aspirin is now rarely used as an anti-inflammatory medication. استخدامه بشكل أساسي ك مبيع وليس ك مسكن
- Its primary use is as anti-platelet drug. مقارنة مع باقي ال NSAIDs
- Because aspirin inhibits platelet aggregation and a prolonged bleeding time, aspirin should not be taken for at least 1 week prior to surgery.

كونه الأسبرين بنستعمله ك antiplatelet ف لحتى ما يصير نزيف بنطلب من المريض يوقف الأسبرين قبل بأسبوع من العملية الجراحية

Dose-dependent effects of salicylates



هون بعرضي ال side effects لل
Salicylate including aspirin
عند:

● الجرعة المنخفضة : gastric
bleeding, impaired blood
clotting, hypersensitivity
reactions

● الجرعة المتوسطة : Tinnitus,
central hyper ventilation

● الجرعة العالية : vasomotor
collapse, Coma ,
Dehydration

Salicylate toxicity

في عتًا ال toxicity ممكن يكون mild في حال الجرعات المنخفضة
وفي عتًا ال severe عند الجرعات العالية ، شوفوا كل وحدة وشو أعراضها

- Salicylate intoxication may be mild or severe.
- The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).
- When large doses of salicylate are administered severe salicylate intoxication may result. The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure.

Reye syndrome

- **Aspirin and other salicylates given during viral infections** have been associated with an increased incidence of **Reye syndrome**, which is an often fatal, fulminating hepatitis with cerebral edema.
- This is especially encountered in children, who, therefore, should be given acetaminophen instead of aspirin when such medication is required to reduce fever. **Ibuprofen** is also appropriate.

إذا الأطفال أو الأشخاص الصغيرة بالعمر كات عندهم **viral infection** ممنوع نعطهم أسبرين ك مسكن او خافض حرارة لأنهم يكونوا معرضين لخطر الإصابة ب **Reye syndrome** وغالباً بتكون **fatal, fulminating hepatitis, cerebral edema**

ف الأنسب من الأسبرين بهيك حالة هو ال **acetaminophen as Panadol** أو **Ibuprofen as Jofen**

Aspirin-induced asthma

الناس إلي معها ربو **asthmatic** ما لازم ياخدوا اسبرين عشان ما يعمللهم **bronchoconstriction** وأعراض تانية نتيجة إفراز الهيستامين مثل احمرار و **abdominal cramping**

- It has long been known that 5–10% of asthmatics are exquisitely sensitive to aspirin, so that ingestion of even a very small dose causes profound bronchoconstriction and symptoms of systemic release of histamine, such as flushing and abdominal cramping.
- Because this reaction to aspirin is not associated with any evidence of allergic sensitization to aspirin or its metabolites and because it is **هاد السبب :** produced by any of the NSAIDs, it is thought to result from inhibition of prostaglandin synthetase (cyclooxygenase), shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway.
- Support for this idea was provided by the demonstration that leukotriene pathway inhibitors impressively reduce the response to aspirin challenge and improve overall control of asthma on a day-to-day basis.

Salicylate Drug Interactions

كونه الأسبرين كثير يرتبط بالبروتين ٨٠ ل ٩٠% ف رح يحل مكان الأدوية إلي يرتبط

- Salicylate is roughly 80% to 90% plasma protein bound (albumin).
 - Aspirin can displace other highly protein-bound drugs, such as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of these agents.

باعتبار الأسبرين **organic acid** ف أكيد ح يصيرله **excretion** **in urine** وهاد يعني أنه ح يآثر عال **uric acid** بالطريقة :

- Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion.
 - At low doses of aspirin (less than 2 g/day), uric acid secretion is decreased,
 - whereas at high doses, uric acid secretion may be unchanged or increased.
- Therefore, aspirin is avoided in gout or in patients taking probenecid.

ما بنعطيه لمرضى التقرس **gout** أو إلي بياخدوا **probenecid** بسبب تراكم ال **uric acid**

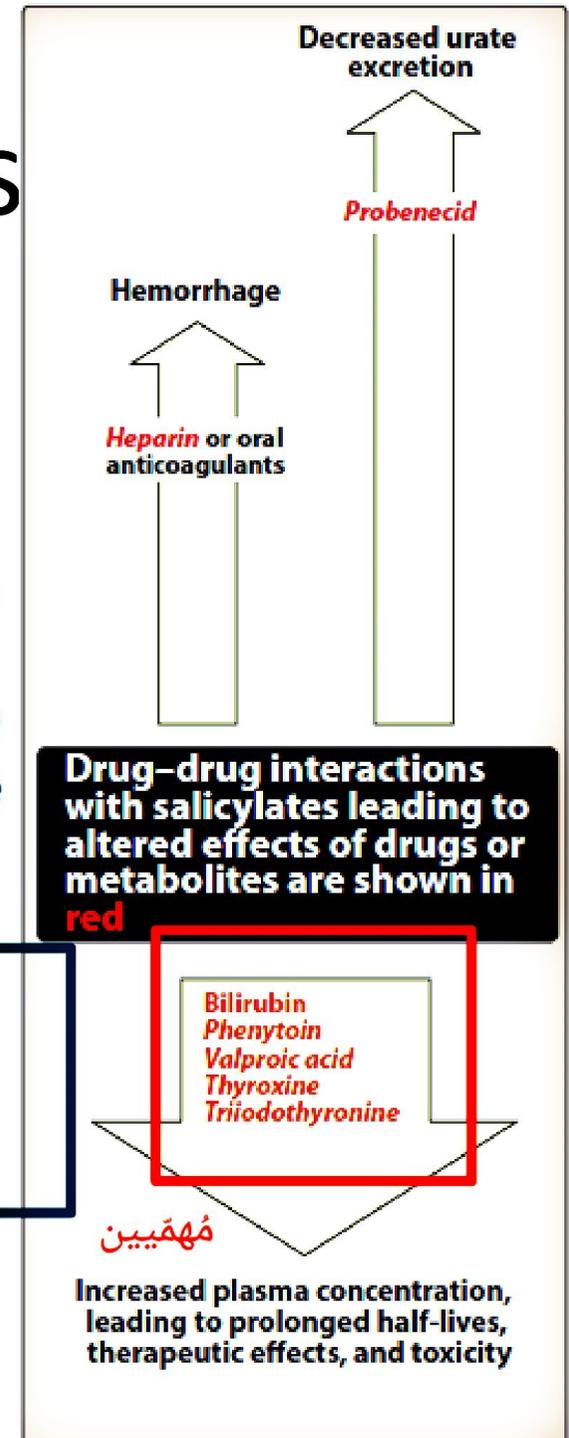


Figure 36.13

Drugs interacting with salicylates.

Propionic acid derivatives

ال propionic acid يشمل مجموعة أدوية وأولها ال **Ibuprofen** من هاي الأدوية :

- **Ibuprofen** was the first in this class of agents to become available in the United States. It has been joined by **naproxen, fenoprofen, ketoprofen, flurbiprofen, and oxaprozin**.
- All of these drugs possess anti-inflammatory, analgesic, and anti-pyretic activity.

بشغلوا ك مسكن وخافض للحرارة ومضاد للالتهابات

- All are well absorbed on oral administration.
- Oxaprozin has the longest half-life and is administered once daily.
- Ibuprofen is used IV to close a patent ductus

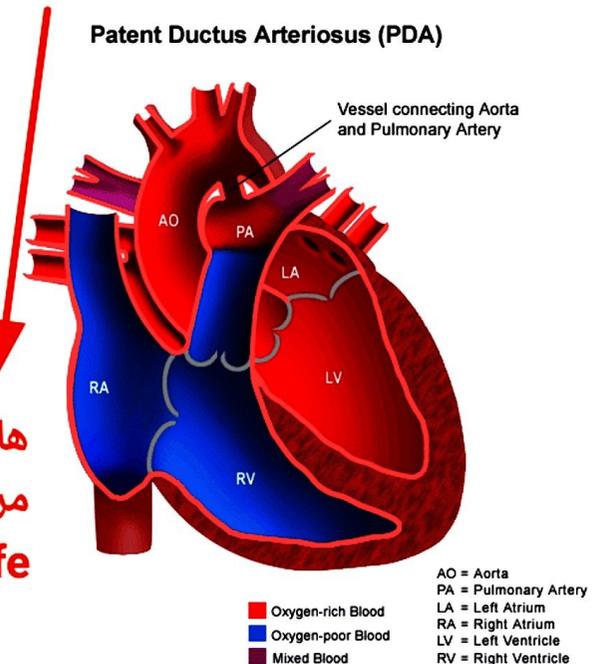
arteriosus (PDA). Patent ductus arteriosus

is a congenital disorder in the heart wherein

a neonate's ductus arteriosus fails to close after birth.

بنستخدم ال **Ibuprofen as IV**
عند ال neonate في حالة ال
PDA

هاي معلومة جدًا مهمة إنه بيتأخذ
مرة وحدة في اليوم لأنه عنده
long half life



مش موجودة as OTC لأنه ال Toxicity إليها أعلى من باقي ال NSAIDs

Acetic acid derivatives

من الأمثلة على ال acetic acid derivative:

- This group of drugs includes indomethacin, sulindac, tolmetin and etodolac.

ما بنسخدم ال tolmetin لعلاج النقرس

أشهر واحد فيهم ال indomethacin ، استخداماته :

Indomethacin uses:

1. An ophthalmic preparation is efficacious for conjunctival inflammation and to reduce pain after traumatic corneal abrasion. تخفيف الألم بعد تآكل القرنية
2. Gingival inflammation is reduced after administration of indomethacin oral rinse. بقلل إلتهاب اللثة
3. Epidural injections produce a degree of pain relief similar to that achieved with methylprednisolone in post laminectomy syndrome (chronic back and/or leg pain that occurs after spinal surgery).

إبر الظهر ، وبتعطينا نفس النتيجة إلي بتعطينا إياها إبرة

post laminectomy syndrome ال حالة ال methylprednisolone

COX-2 selective inhibitors

- COX-2 selective inhibitors (**celecoxib** and **meloxicam**) were developed in an attempt to inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active “housekeeping” COX-1 isozyme found in the GI tract, kidneys, and platelets.
- They selectively bind to and block the active site of the COX-2 enzyme much more effectively than that of COX-1.
- **Celecoxib** was the first member of a newer NSAID subgroup, the cyclooxygenase-2 (COX-2)-selective inhibitors, which were developed in an attempt to lessen the gastrointestinal toxicity associated with COX inhibition while preserving efficacy. Unfortunately, clinical trials involving some of the highly selective COX-2 inhibitors have shown a higher incidence of cardiovascular thrombotic events than the nonselective drugs.

celecoxib ← COX2 selective
meloxicam ←

كيف يستعمل؟
inhibition لتكوين prostaglandins
على طريق
إنزيم COX 2 بدون ما يؤثر على إنزيم COX 1
الوجود في
Platelets, Kidneys, GI tract

× ما هي الأدوية التي ترتبط بال active site
من COX 2 ويحل بولك إن

× طبقاً إلى celecoxib هو أول دواء موجود في ال NSAIDs
COX 2 selective inhibitor
التي لها نسبة أقل من ال NSAIDs
وذلك يعني أنها أقل خطراً على القلب
حيث إنها ترتبط cardiovascular thrombotic أكثر من باقي ال NSAIDs

COX-2 selective inhibitors

- COX-2 inhibitors have analgesic, antipyretic, and anti-inflammatory effects similar to those of non-selective NSAIDs but with an approximate halving of GI adverse effects.
- However, because COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs.
- **Rofecoxib** and **valdecoxib**, two previously marketed, selective COX-2 inhibitors, were withdrawn from the market because of their association with increased cardiovascular thrombotic events.

* Therapeutic effect لهي الوجود هو : analgesic, antipyretic, anti-inflammatory effect

← يعني نفس الـ effects بتعطي NSAIDs non-selective لكن ضررها على الـ GI أقل

* توجد الـ COX2 موجود بالـ kidneys ويمكن ان يكون الـ renal toxicity

* بالـ selective COX2 inhibitors مثل celecoxib, rofecoxib بتسبب الـ cardiovascular thrombotic events

الاستنتاج ان الـ selective COX2 inhibitors وليست non-selective

Therapeutic disadvantages of selected NSAIDs*

Upper GI disturbances are common

No antipyretic effect

Very potent; should be used only after less toxic agents have proven ineffective

CNS disturbances are common

Potential for increasing myocardial infarctions and strokes

Salicylates:

Aspirin
Salicylate salts
Diflunisal

Acetic acids:

Indomethacin
Sulindac
Tolmetin

Propionic acids:

Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin

Oxicams:

Piroxicam
Meloxicam

Fenamates:

Mefenamic acid
Meclofenamic acid

COX-2 Inhibitors

Celecoxib

Therapeutic advantages of selected NSAIDs

Low cost; long history of safety

Less GI Irritation than aspirin

Long half-life permits daily or twice daily dosing

Lower toxicity and better acceptance in some patients. *Naproxen* is considered by some experts as one of the safest NSAIDs

Less GI Irritation than *aspirin*

Choice of NSAIDs

كلهم الهم نفس الفعالية مثل ما حكينا سابقًا إنه اختلافهم بال **side effects** ، بس ولكن في استثناءات :

- All NSAIDs, including aspirin, are about equally efficacious with a few exceptions:
 - Tolmetin seems not to be effective for gout ما بنستخدمه بالنقرس
 - Diflunisal does not have antipyretic effect ما إله تأثير ك خافض حرارة
- Thus, NSAIDs tend to be differentiated on the basis of toxicity and cost-effectiveness. For example, the GI and renal side effects of ketorolac limit its use. بختلفوا بال **toxicity** والتكلفة ، آثار الدوا الجانبية على الكلى وال GI برضو مهم اخذها بعين الاعتبار .
- Some surveys suggest that indomethacin and tolmetin are the NSAIDs associated with the greatest toxicity, while ibuprofen is the least toxic.

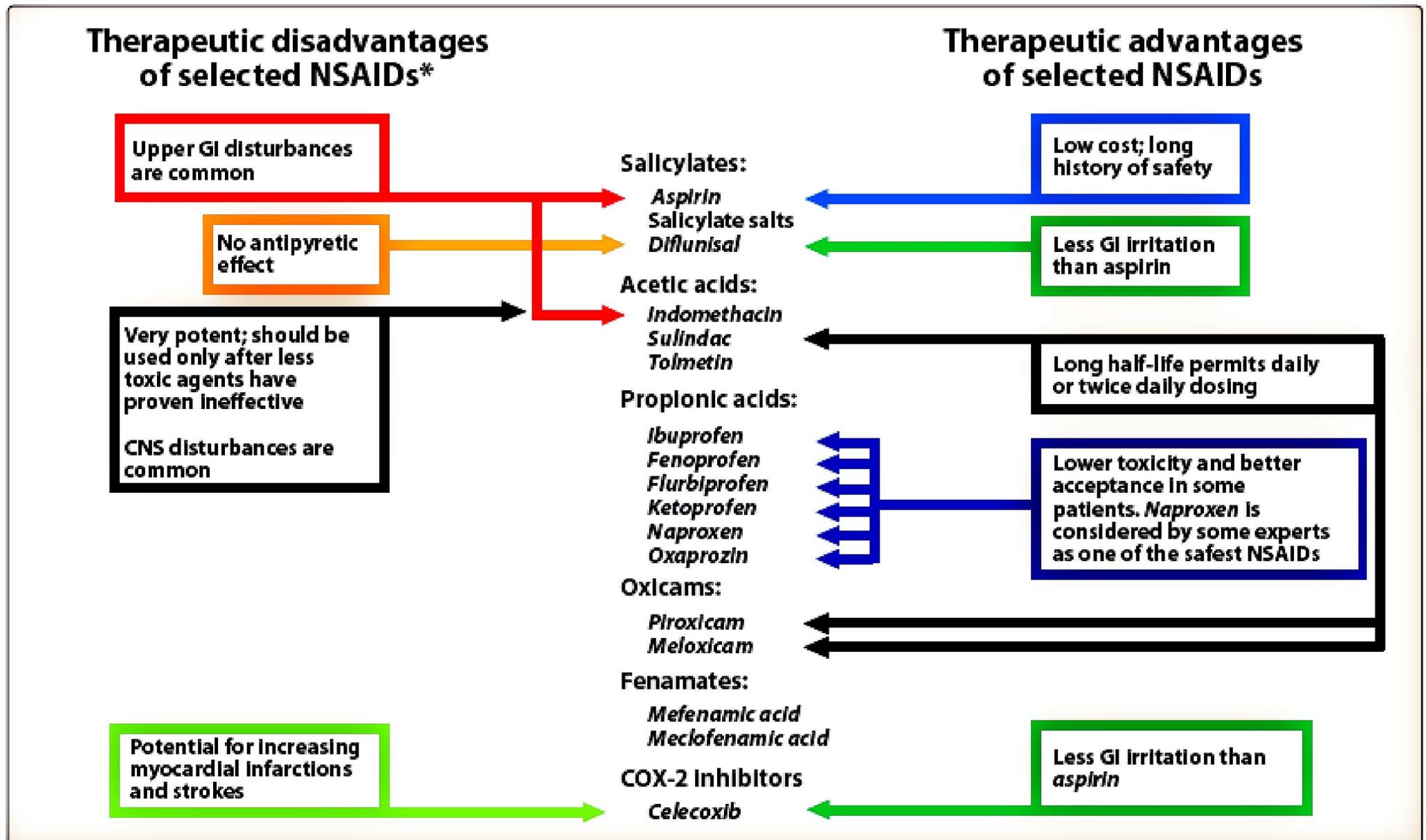
indomethacin, tolmetin -----> High toxicity

Ibuprofen ----> least toxicity

Choice of NSAIDs

- The relatively expensive, selective COX-2 inhibitor celecoxib is probably safest for patients at high risk for GI bleeding but may have a higher risk of cardiovascular toxicity.
يُعتبر غالبي مقارنة بباقي ال NSAIDs لكنه أكثر شي safe ع
مرضى ال high risk GI bleeding لكن إله خطر عالقلب
- Celecoxib or a nonselective NSAID plus omeprazole or misoprostol may be appropriate in patients at highest risk for GI bleeding; in this subpopulation of patients, they are cost-effective despite their high acquisition costs.
non selective COX2 inhibitor+ Omeprazole/ misoprostol
high risk GI bleeding أحسن شي لمرضى ال --->
لكن سلبيته حط خط عندها
- The choice of an NSAID thus requires a balance of efficacy, cost-effectiveness, safety, and numerous personal factors (eg, other drugs also being used, concurrent illness, compliance, medical insurance coverage), so that there is no best NSAID for all patients.
أسس اختيار أدوية ال NSAIDs المناسبة :

ايجابيات وسلبيات كل چروب من ال NSAIDs:



Acetaminophen

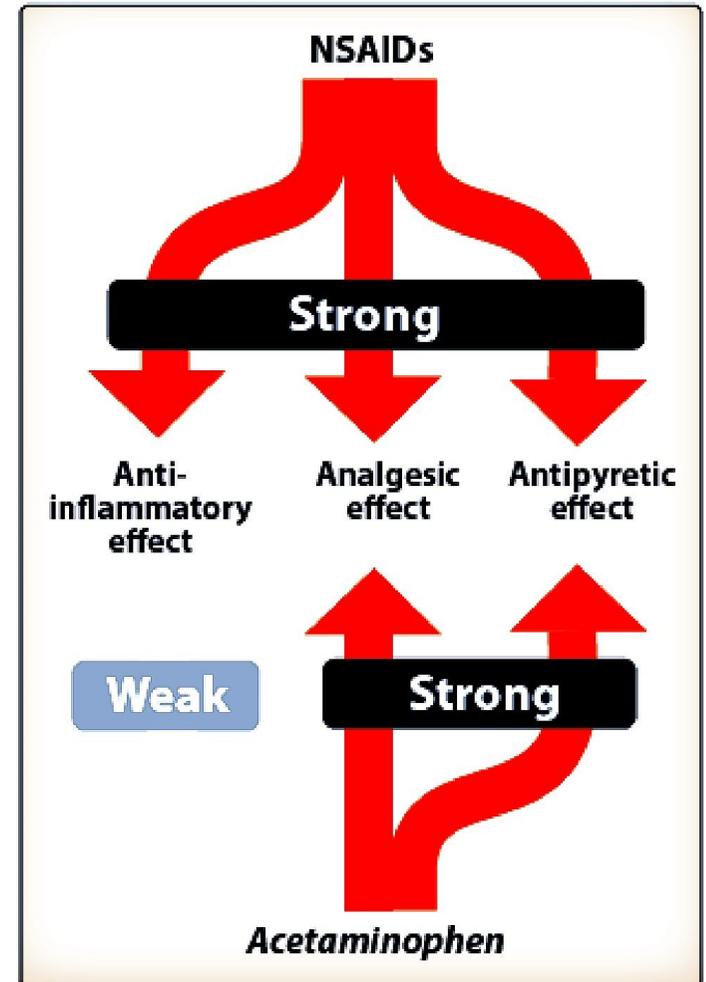
لا يُستخدم ك anti inflammatory
بنالقيه ب dosage form as IV

- Acetaminophen (paracetamol) is one of the most important drugs used in the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary.

Pharmacokinetics

- Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying, and peak blood concentrations are usually reached in 30–60 minutes.
- The half-life of acetaminophen is 2–3 hours and is relatively unaffected by renal function.
- The drug is also available in intravenous and rectal formulations.

ما حدا فينا ما بيعرف البنادول
أبسط مثال ، السلايد سهل
ركزوا عالتخطيط



Acetaminophen

Mechanism of Action

مش معروفة الآلية إلي بشتغل فيها

- The mechanism of analgesic action of acetaminophen is unclear.
- The drug is only a weak COX-1 and COX-2 inhibitor in peripheral tissues, which accounts for its lack of anti-inflammatory effect.
- Evidence suggests that acetaminophen may inhibit a third enzyme, COX-3, in the CNS.

Effects

- Acetaminophen is an analgesic and antipyretic agent; it lacks antiinflammatory or antiplatelet effects.

بشتغل ك مسكن وخافض للحرارة لكن ضعيف
جدا ك anti inflammatory and
antiplatelet

بشتغل ك COX2 inhibitor، COX1 بس في
دراسات بتحكي إنه بشتغل على برضو COX3 in
the CNS وهاد دليل إنه ما في منه توبيكال ، لأنه
شغله systemic

Acetaminophen

بنستخدمه بعلاج آلام بسيطة مثل
الصداع وآلم الظهر وآلم بعد الولادة

Indications:

- The drug is useful in mild to moderate pain such as headache, myalgia, postpartum pain. **يُعتبر خيار في حال الشخص عنده حساسية من الأسبرين أو tolerated**
- For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated.
- It is preferable to aspirin in patients with hemophilia or a history of peptic ulcer and in those in whom bronchospasm is precipitated by aspirin.
- Acetaminophen alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to anti-inflammatory therapy. **لا يُعتبر علاج كافٍ في حالة ال RA**
- It is preferred to aspirin in children with viral infections.

Dosage

حكينا الأسييتامينوفين والأيبوبروفين بدل الأسبرين بحالة ال **viral infection**

- Acute pain and fever may be effectively treated with 325–500 mg four times daily and proportionately less for children.
- Dosing in adults is now recommended not to exceed 4 g/d, in most cases.

ال **toxic dose** منه هي 4g باليوم

Acetaminophen

Toxicity:

- In therapeutic dosages, acetaminophen has negligible toxicity in most persons.
- However, when taken in overdose or by patients with severe liver impairment, the drug is a dangerous hepatotoxin.
- Early symptoms of hepatic damage include nausea, vomiting, diarrhea, and abdominal pain.
- Doses greater than 4 g/d are not usually recommended and a history of alcoholism contraindicates even this dose.

بحكيك إنه إذا الشخص اخذ او قر دوز منه أو كان عنده مشاكل بالكبد ف هو معرّض
يصير معه hepatotoxin و إلي يكون إلها أعراض بالبداية مثل **nausea, vomiting,**
diarrhea, abdominal pain
ما لازم الواحد يتعدّى ال 4g منه باليوم الواحد