Non steroidal anti-inflammatory drugs

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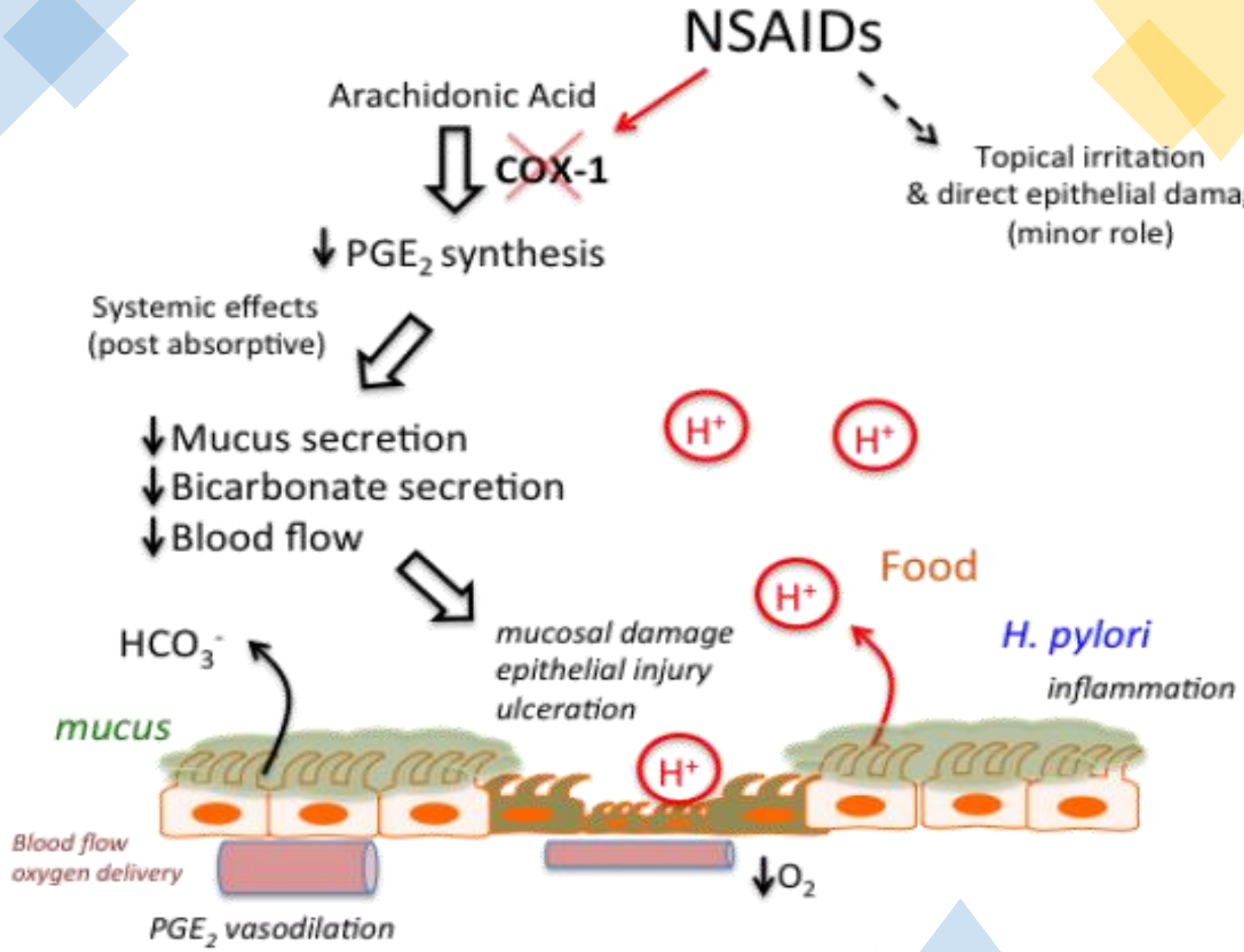
Adverse effects of NSAIDs:

A. Gastrointestinal (GIT irritation):

- These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding.
- More common with agents with a higher relative selectivity for COX-1.
- Inhibition of COX-1 in the stomach → reduces prostaglandins, resulting in increased gastric acid secretion, diminished mucus and bicarbonate production → increased risk for gastrointestinal bleeding and ulceration.


NSAIDs
Arachidonic Acid
COX-1
Topical irritation
& direct epithelial damage
(minor role)
↓ PGE2 synthesis
Systemic effects
(post absorptive)
↓Mucus secretion
↓Bicarbonate secretion
↓Blood flow
H+
H+
H+
H+
Food
HCO3-
mucosal damage
epithelial injury
ulceration
H. pylori
inflammation
mucus
Blood flow
oxygen delivery
↓O2
PGE2 vasodilation

- **To diminish NSAIDs-induced GIT irritation:**

i. **NSAIDs should be taken after a meal.**

ii. **If NSAIDs are used in patients at high risk for GI events, proton pump inhibitors or misoprostol should be used concomitantly to prevent NSAID-induced ulcers.**

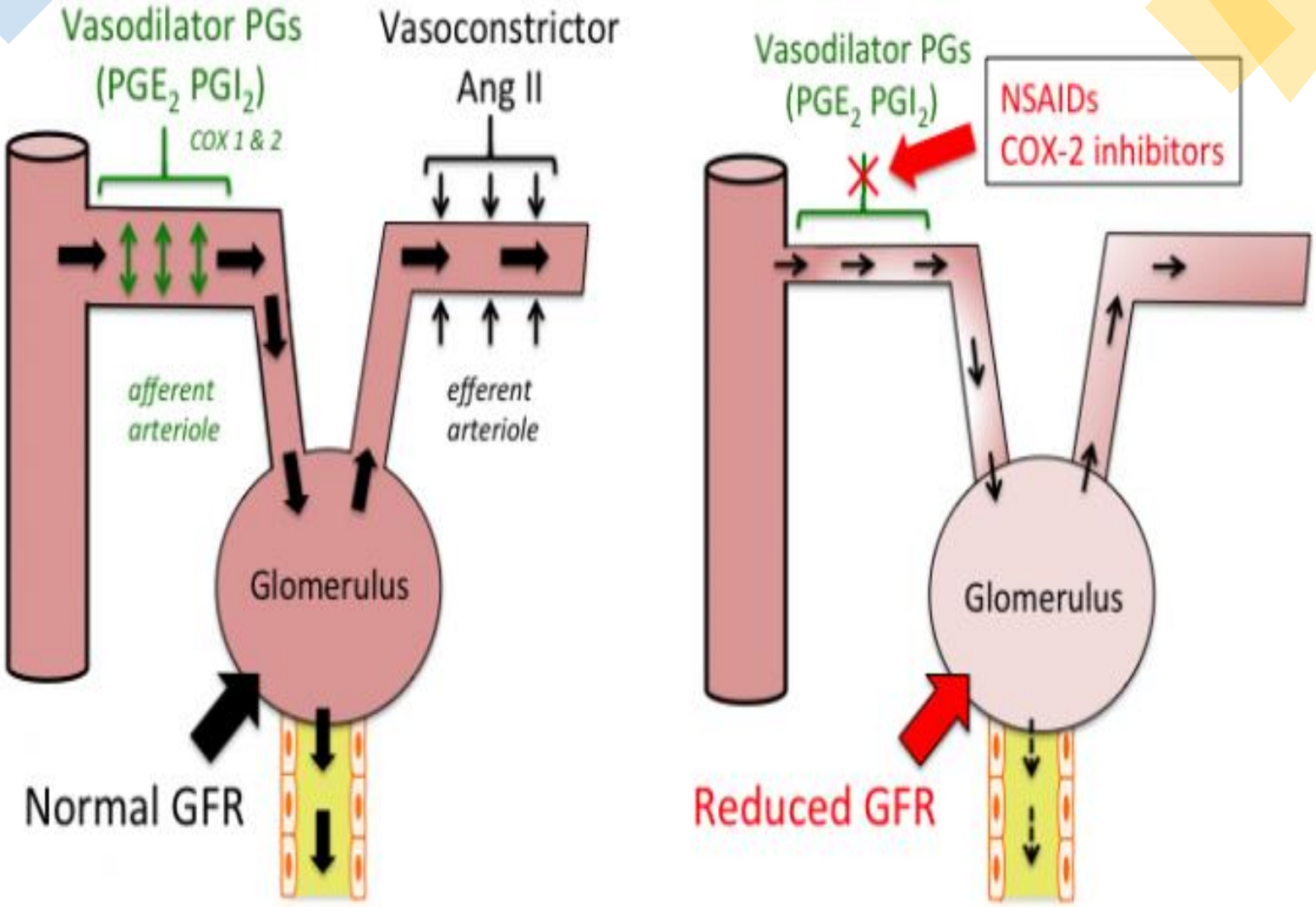
iii. **Switch to COX-2 inhibitors (celecoxib)**

B. Increased risk of bleeding:

- **Aspirin prolongs bleeding time by its antiplatelet effect.**
- **For this reason, aspirin is often withheld for at least 1 week before surgery.**

C. Renal effects:

1) **NSAIDs decrease renal synthesis of prostaglandins, resulting in retention of sodium and water, and may cause edema.**
- **Patients with a history of heart failure or kidney disease are at particularly high risk.**
2) **NSAIDs can be nephrotoxic and can cause interstitial nephritis.**


Vasodilator PGs
(PGE2 PGI2)
COX 1 & 2
Vasoconstrictor
Ang II
afferent
arteriole
efferent
arteriole
Glomerulus
Normal GFR
Vasodilator PGs
(PGE2 PGI2)
NSAIDs
COX-2 inhibitors
Glomerulus
Reduced GFR

D. **Bronchospasm:**

- **NSAIDs → inhibit the synthesis of prostaglandins and cause a shift toward leukotriene production → increase the risk of asthma exacerbations.**

E. **Hypersensitivity reactions [urticaria, bronchoconstriction, and angioedema].**

F. **Idiosyncrasy: hemolytic anemia in patients with G6PD deficiency (favism).**

G. **Phenylbutazone can cause neutropenia and aplastic anemia.**

H. **Teratogenicity:**

i. **NSAIDs use in pregnancy can cause cardiac septal defect. [Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.]**

ii. **In the third trimester, NSAIDs should be avoided due to the risk of premature closure of the ductus arteriosus.**

I. **Reye's syndrome**

Toxicity:

Salicylism [chronic salicylate toxicity]: (reversible and dose dependent)

- Mild salicylate toxicity occurs due to the use of a large dose for a long time.
- It is characterized by:
  i. Nausea and vomiting. Due to git irritation
  ii. Marked hyperventilation. (respiratory alkalosis) due to + R.C
  iii. Headache, mental confusion, and dizziness.
  iv. Blurred vision.
  v. Tinnitus (ringing or roaring in the ears). Ist sign of salicylism.
  vi. Metabolic acidosis (later) due to + lactate production.

Acute Severe Salicylate Intoxication:

- **When high doses of salicylate are administered (more common in children), it may result in:**
  - **Restlessness, delirium, hallucinations, convulsions, and coma.**
  - **Hyperacidity & GIT irritation: nausea, vomiting, pain, ulcer & bleeding.**
  - **Hypoprothrombinemia.**
  - **Hyperpyrexia, hyperventilation & hyperhidrosis → dehydration.**
  - **Respiratory alkalosis (early)and metabolic acidosis (late).**
  - **Death from respiratory failure (RC depression) may occur.**

Management of Acute Toxicity

1) **Symptomatic treatment:**
   i. **Cooling fomentation (cold water or alcohol) for hyperpyrexia.**
   ii. **Correction of dehydration & acid-base imbalance by fluids and sodium bicarbonate.**
   iii. **Vitamin K or blood transfusion for hemorrhage.**
2) **Alkalization of urine by sodium bicarbonate**
3) **Hemodialysis in severe cases.**

Contraindications of NSAIDs:

1) Allergy.
2) G6PD deficiency (Favism).
3) Bleeding tendency.
4) Bronchial asthma.
5) Peptic ulcer.
6) Pregnancy.
7) Children with viral infections (cause Reye's syndrome).
8) Aspirin is not used in Gout in small dose.

Drug interactions

1) Salicylate can be displaced from protein-binding sites by other drugs, resulting in increased concentration of free salicylate.
2) Alternatively, aspirin can displace other highly protein-bound drugs, such as warfarin, phenytoin, oral hypoglycemic, or valproic acid, resulting in higher free concentrations of these agents.
3) Compete with other uricosurics, e.g., probencid & phenylbutazone.
4) Barbiturates potentiate the analgesic effect of salicylates.
5) Increase incidence of peptic ulcer if with other anti-rheumatics & corticosteroids.

6) **Concomitant use of NSAIDs and aspirin should be avoided because this can prevent aspirin from binding to cyclooxygenase and interfere with its antiplatelet effect.**

7) **NSAIDs reduce the beneficial effects of antihypertensive medications.**

8) **NSAIDs antagonize the action of diuretics and can cause fluid retention.**

9) **NSAIDs increase the risk of hyperkalaemia caused by ACE inhibitors.**

Selective COX-2 inhibitors
Celecoxib

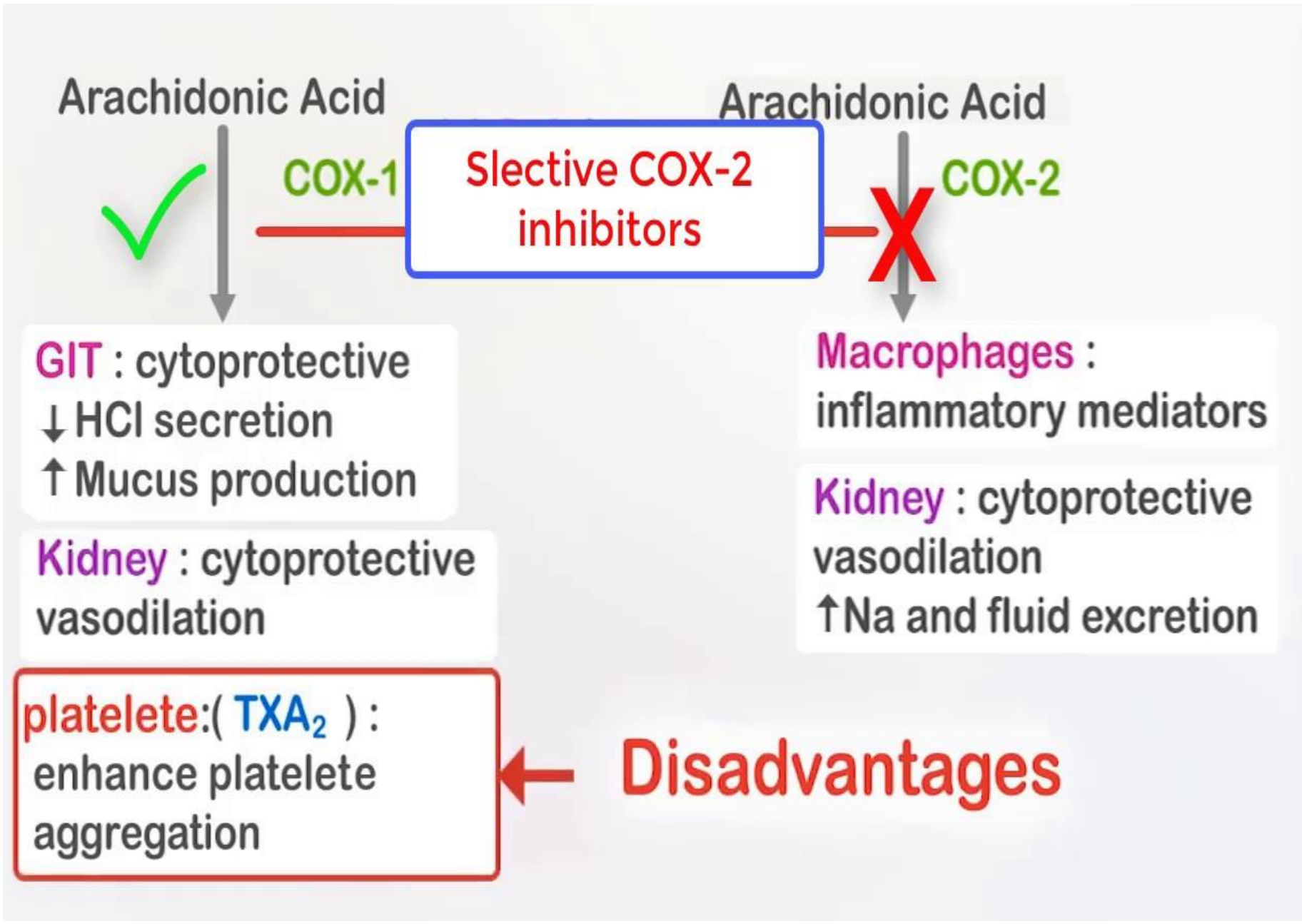
Pharmacokinetics:

- Celecoxib is readily absorbed after oral administration.
- It is extensively metabolized in the liver by cytochrome P450 (CYP2C9), and the metabolites are excreted in feces and urine.
- The half-life is about 11 hours, and the drug may be given once or twice daily.
- The dosage should be reduced in those with moderate hepatic impairment, and celecoxib should be avoided in patients with severe hepatic or renal disease.
- Inhibitors of CYP2C9, such as fluconazole, may increase serum levels of celecoxib.

Therapeutic uses:

- **Celecoxib has similar efficacy to NSAIDs and is approved for the treatment of:**

1) **Rheumatoid arthritis**
2) **Osteoarthritis**
3) **Acute pain**


Arachidonic Acid
COX-1
Slective COX-2 inhibitors
Arachidonic Acid
COX-2
GIT : cytoprotective
↓HCl secretion
↑Mucus production
Kidney : cytoprotective
vasodilation
platelete:(TXA2) :
enhance platelete aggregation
Macrophages :
inflammatory mediators
Kidney : cytoprotective
vasodilation
↑Na and fluid excretion
Disadvantages

Adverse effects of selective COX-2 inhibitors:

1) **Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. Celecoxib is associated with less GI bleeding and dyspepsia than other NSAIDs.**
2) **Increased cardiovascular events (possibly by decreasing PGI_2 production mediated by COX-2).**
3) **Hypersensitivity reactions.**

References

- **Wilkins R, Cross S, Megson L and Meredith D (2011)**: Oxford Handbook of Medical Sciences Second Edition.
- **Tao Le, Vikas Bhushan Matthew Sochat, Yash Chavda, Kimberly Kallianos, Jordan Abrams, Mehboob Kalani and Vaishnavi Vaidyanathan (2019)**: FIRST AID for the USMLE Step 1.
- **Sandra K. Leeper-Woodford and Linda R. Adkison (2016):** Lippincott Illustrated Reviews: Integrated Systems.
- **Duncan Richards, Jeffrey Aronson, D. John Reynolds, and Jamie Coleman (2012):** Oxford Handbook of Practical Drug Therapy. NSAIDs. Pages 658-665.


Thank You