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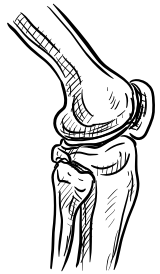

PHARMACOLOGY

MID | Lecture #4

NSAIDs (pt.3)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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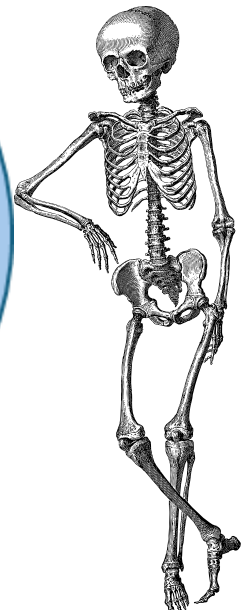

رَمَضَانُ مُبَارَكٌ

REMEMBER FROM GENERAL PHARMACOLOGY

- Where do drug-drug interactions occur?

1. Absorption (Pharmacokinetics)
2. Distribution (Pharmacokinetics)
3. Metabolism (Pharmacokinetics)
4. Excretion (Pharmacokinetics)
5. Receptors (Pharmacodynamics)

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Drug interactions:

- Salicylate is 90 to 95 percent 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**, **phenytoin**, or **valproic** acid, resulting in higher free concentrations of the other agent .

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

- Aspirin is a type of salicylate, and in the body, it is converted into salicylic acid, making their effect similar.

Warfarin: anti coagulant
phenytoin: antiepileptic
valproic: antiepileptic
ketorolac: NSAID

this tells that no matter what is the effect of other drug toxicity and adverse effects of salicylate increases, due to competition with other drugs at interaction and [free drug] increase.

- Salicylate is 90-95% protein-bound, meaning that, only a small portion is free. The free drug (10%) is the active form that reaches circulation and produces effects, whether antiplatelet or anti-inflammatory.
- Drugs that compete for plasma protein binding can increase the free concentration of other bound drugs, raising the risk of toxicity. For example, Aspirin displaces Warfarin from its bound protein, increasing free Warfarin levels. This enhances its anticoagulant effect, raising the bleeding risk. Monitoring and dose adjustment may be needed.

Toxicity:

The mild form is called salicylism

What are the symptoms of aspirin overdose?

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

Aspirin has a direct effect on the respiratory center in the brain leading to hyperventilation. The body responds to hyperventilation by having the kidneys produce more bicarbonate and excrete more potassium which leads to an elevated anion gap metabolic acidosis.

In serious cases, mandatory measures include the intravenous administration of **fluid**, **dialysis** correction of **acid-base** and electrolyte balances.

- High Aspirin Dose → Stimulates Respiratory Center → Hyperventilation → Excess CO2 Loss → ↓ H_2CO_3 → Respiratory Alkalosis → Continued Exposure to Aspirin → Uncoupling of Oxidative Phosphorylation →↑ Lactic Acid → Metabolic Acidosis

↓ $CO_2+H_2O \rightleftharpoons$ ↓ H_2CO_3

$H_2CO_3 \leftarrow H^+$↓ $+HCO_3^-$ alkalosis

- Treatment:

✓Activated charcoal binds aspirin in the gut, preventing absorption and reducing toxicity. It is most effective when given within one hour of ingestion.

✓urinary alkylation to achieve acid-base and electrolyte balances.

✓intravenous administration of fluid

✓dialysis

Toxic effects of aspirin on respiratory center

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis
- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased oxygen utilization and glucose demand, increased glyconeogenesis, and increased heat production
- (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids
- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

Bro, I know this table looks like a final boss fight, but don't worry—I got you. We're breaking it down in the next slides 👍🔥😎

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Drugs	Mechanism of action	Side effect	Other notes
Salicylate • *Aspirin*	• Irreversibly inhibits Cyclooxygenase 1 (COX-1) and COX-2 • Inhibition of COX-2 suppresses prostanoid synthesis providing analgesic, anti-pyretic and anti-inflammatory effects • Aspirin is weakly selective to COX-1	• **Gastrointestinal:** Inhibition of COX-1 causes dyspepsia and if severe gastric bleeding and ulceration • **Rashes:** Morbiliform rash, urticaria, toxic epidermal necrolysis (TEN) • **Acute renal failure** • **Increase blood pressure** • **Reduce effect of anti-hypertensives** (except CCB) • Salicylate poisoning in aspirin overdose (hyperventilation, tinnitus, deafness, vasodilatation)	• Contraindicated in active peptic ulceration, bleeding disorders, children under 16 years (risk of Reye's syndrome), severe cardiac failure
Propionate • *Ibuprofen* • *Naproxen*	• Competitive inhibitors of COX-1 and COX-2 • Both ibuprofen and naproxen are weakly selective to COX-1		• Contraindicated in GI bleed, ulceration, heart failure
Coxibs • *Celecoxib* • *Etoricoxib*	• Competitive inhibitor of COX-2 only at therapeutic dose	• Similar to other NSAIDs • Less gastrointestinal side-effects	• Contraindicated in active GI bleed, ulceration, cerebrovascular disease, inflammatory bowel disease, ischemic heart disease, heart failure, peripheral arterial disease • Monitor blood pressure
Paracetamol	• Exact mechanism unknown but has ability to inhibit COX pathways • Good analgesic and anti-pyretic but poor anti-inflammatory effects	• Paracetamol overdose can cause liver damage • Presents with nausea and vomiting, associated with right subcostal pain and tenderness	

GRAM PROJECT

1)Aspirin:

- Aspirin has an antiplatelet effect at low doses. At high doses, it retains its antiplatelet effect while also acting as an antipyretic and anti-inflammatory. Both low and high concentrations increase the risk of bleeding
- Aspirin irreversibly inhibits COX-1 and COX-2, with a higher affinity for COX-1.

2)Ibuprofen and Naproxen:

- used as analgesics for:
  menstrual and tooth pain.
- They cause less gastric irritation than aspirin, making them more commonly used.

3)Celecoxib and Etoricoxib

- Celecoxib and Etoricoxib are competitive inhibitors of COX-2 only at therapeutic doses. At very high doses in laboratory settings, their selectivity may change. However, in clinical use for humans, they remain selective for COX-2
- They have fewer gastrointestinal side effects compared to non-selective NSAIDs. However, they are associated with black box warnings for cerebrovascular diseases, as they increase the risk of stroke and myocardial infarction (MI), so extra caution is required

N.B: A Black Box Warning is the strongest safety warning issued by FDA, Indicating severe adverse effects, such as fatal toxicity, life-threatening conditions, or permanent disability.

4)Paracetamol

- Paracetamol is not an NSAID because it lacks significant anti-inflammatory effects. It acts centrally and is used as a painkiller. While its exact mechanism is unclear, it is believed to inhibit the COX pathway. However, it is a poor anti-inflammatory agent.

Naproxen and Ibuprofen

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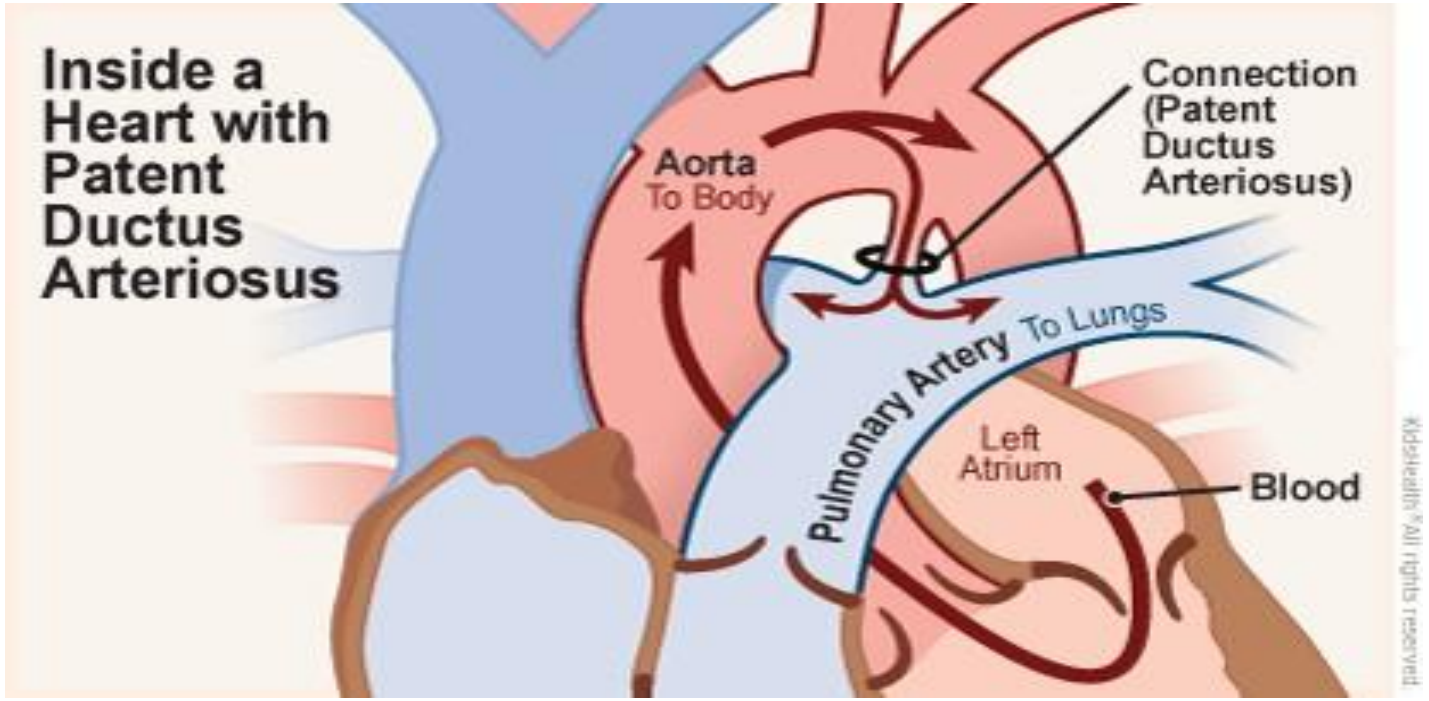
- Pregnancy : category C, category D 3rd trimester
- Increase the risk of cardiovascular thrombotic event, MI and stroke.
- Increase risk of GI bleeding.
- Ibuprofen not exceed 3200mg/day, and take with food or with water to avoid GI effect.
- **Naproxen and Ibuprofen are not completely safe during pregnancy.** In the **first and second trimesters (Category C),** they may pose a risk but can be used if necessary. In the **third trimester (Category D),** they increase the risk of **ductus arteriosus closure and bleeding complications,** so they should be avoided.

Acetic acid derivatives

Indomethacin:

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



- During fetal development, a small blood vessel that connects the pulmonary artery to the aorta called Ductus Arteriosus allows blood to bypass the lungs. This shunt is essential because the fetus does not use its lungs for oxygen exchange. To keep the Ductus Arteriosus open, the body relies on vasodilatory prostaglandins like PGE2. Normally, after birth, when the baby starts breathing, the ductus closes within 12-24 hours and completely seals off in the following weeks.
- In the last months of pregnancy, taking NSAIDs like Ibuprofen or Naproxen lowers PGE2 levels, leading to premature closure of the Ductus Arteriosus, which can cause serious fetal complications.
- On the other hand, some babies are born with a Patent Ductus Arteriosus (PDA), where the shunt remains open after birth. In such cases, Ibuprofen and Indomethacin can be used to help close it (if detected early after birth) .
- If medication fails or the condition is detected later on, the condition can be corrected through surgery.

Oxicam derivatives

Piroxicam *and* ***meloxicam***

- *are used to treat Rheumatoid Arthritis and* osteoarthritis.
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- ***Meloxicam*** *inhibits both COX-1 and COX-2, with preferential binding for COX-2,* and at low to moderate doses shows less GI irritation than *piroxicam.*

Diclofenac sodium

- Used PO 50mg after food, I.M. inj 75mg
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Toxicity similar to others

(فَاذْكُرُونِي أَذْكُرْكُمْ وَاشْكُرُوا لِي وَلَا تَكْفُرُونِ)

Acetaminophen = Paracetamol

- **Weak PG synthesis inhibitor**
- **CNS actions:** Paracetamol also modulates the endogenous cannabinoid system
- **Not:**
  - **anti inflammatory**
  - **Platelets inhibitor**
  - **Ulcerogenic**
  - **Teratogenic**

    (it is not safe for babies or fetus in pregnancy)

-According to Pregnancy Category Paracetamol is considered between A and B (go to slide 29 and 30 to Know categories), which means it is safe. But we should worry about paracetamol, because overdose can cause liver damage

-4 grams a day (1 pill=500mg for adult→ 8 pills) is the maximum dose that we can take form Paracetamol.

Acetaminophen

- Acetaminophen inhibits prostaglandin synthesis in the **CNS**.

  This explains its antipyretic and analgesic properties.

  Why it is not anti-infalmmatory?

  - Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its **weak** anti-inflammatory activity.
  - Acetaminophen does not affect **platelet** function or increase blood clotting time.

Therapeutic uses

- 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

➢ or those who do not 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** a highly reactive and potentially dangerous metabolite . That's why overdose of paracetamol can cause liver damage.

- **N- acetylbenzoiminoquinone (NAPQI)**: is not active, but it is highly reactive.
  - **Highly Reactive (NAPQI)**: It can quickly react with cell components, especially **proteins and lipids**, leading to **cell damage→ haptic damage**
  - **Not Active (NAPQI)**: It does not have a **therapeutic effect**, but it causes **liver damage** when it accumulates at toxic doses.

- How body can get rid form **NAPQI?**

By Glutathione Reduction System, we have an enzyme that convert **NAPQI** by interaction with SH group into an inactive metabolite.

- What dose happen when too much Paracetamol is taken?

The glutathion system in the body will be overwhelemd → is not able to reduce this extra metabolite→ accumulate in hepatocytes start killing them .

Adverse effects

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

- large doses leads to Hepatic necrosis, a very serious and potentially life-threatening condition can result.

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

  A patient taking paracetamol for long period of time at high dose (not toxic dose), will have elevation in liver enzymes in blood (an indicator of liver damage). maximum tolerated dose which is **4mg/day** must not be exceeded

- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy

فَذَكِّرْ بِالْقُرْآنِ مَن يَخَافُ وَعِيدِ

Acetoaminophen

- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of **glutathione**, forming a nontoxic substance.

- Acetaminophen and its metabolites are excreted in the urine.

- **Toxicity**
  - **Severe hepatotoxicity with high doses**
  - **N- acetylcysteine is the antidote (the treatment) when given in the first 24hours to avoid permanent liver damage.**

Cyclooxygenase II Inhibitors: Celecoxib

- 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.

- COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs

Cyclooxygenase II Inhibitors: Celecoxib cont.

- a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1.

- It interacts occasionally with warfarin—as would be expected of a drug metabolized via CYP2C9

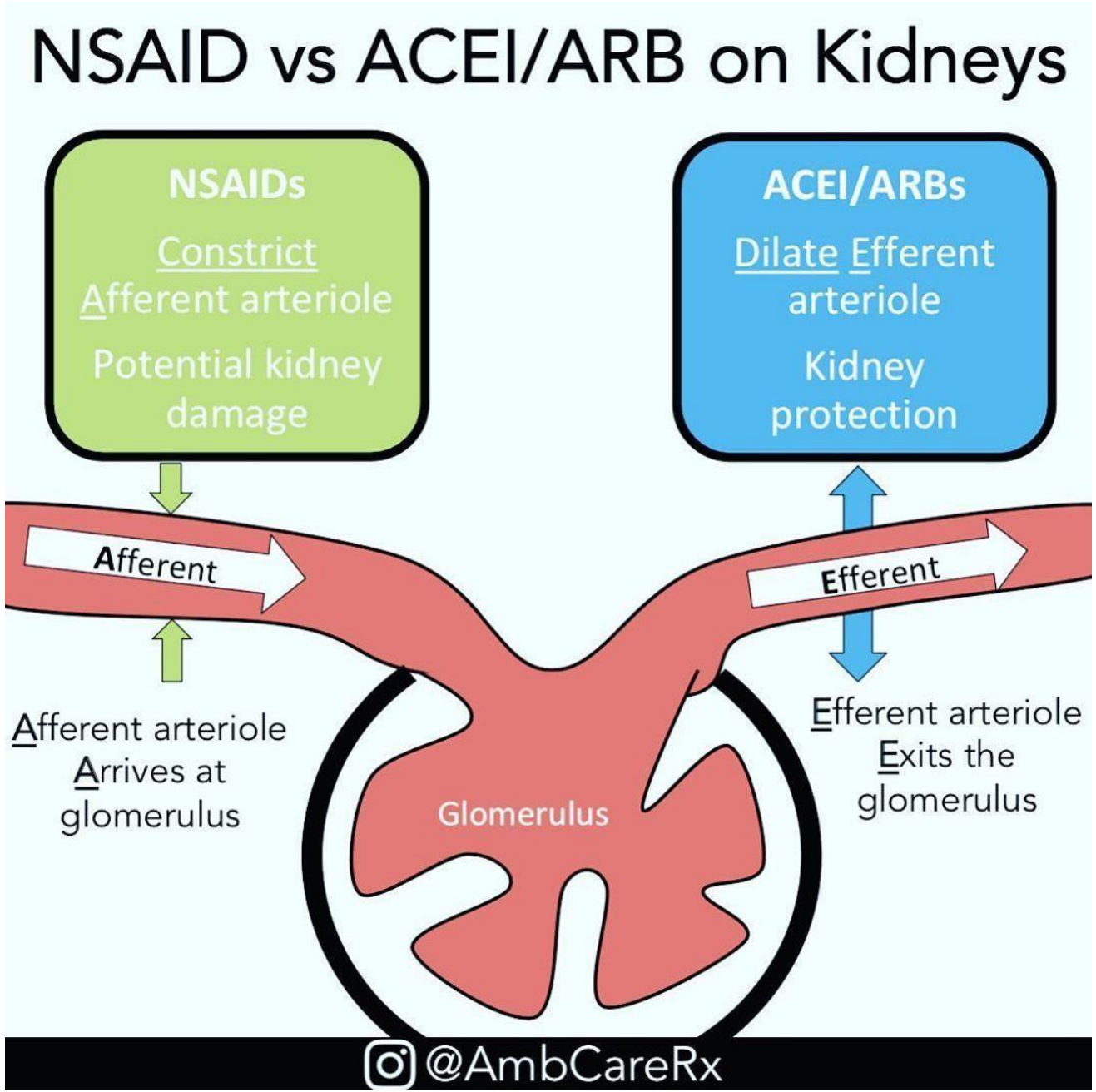
- Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib, resulting in their withdrawal from the market.

FDA Pregnancy Categories

Category	Interpretation
A	Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans: Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.
D	Positive evidence of risk: Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh risks.
X	Contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

·**A**: Safe, no proven risk.
·**B**: No evidence of risk in humans, but may show in animals.
·**C**: Risk cannot be ruled out, but benefits may justify use.
·**D**: Proven risk, but benefits may outweigh it.
·**X**: Confirmed risk, contraindicated in pregnancy.

- Generally, A and B are safe.
- C: we have to think about it and try to find alternative that is safer.
- X: never use, if the mother takes a drug that is in category X, we are almost sure that the upcoming fetus will have a teratogenicity.


NSAID vs ACEI/ARB on Kidneys
NSAIDs
Constrict Afferent arteriole
Potential kidney damage
ACEI/ARBs
Dilate Efferent arteriole
Kidney protection
Afferent
Efferent
Afferent arteriole Arrives at glomerulus
Glomerulus
Efferent arteriole Exits the glomerulus
@AmbCareRx

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إِنْ تَلْقَهُ الأُسْدُ فِي آجَامِهَا تَجِمِ

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Katzung-basic & clinical pharmacology chapter 36

﴿ إِنَّ وَلِيِّيَ اللَّهُ الَّذِي نَزَّلَ الْكِتَابَ ۖ وَهُوَ يَتَوَلَّى الصَّالِحِينَ﴾

اللَّهُمَ صَلِّ صَلَاةً كَامِلَةً، وَسَلِّم سَلَامًا تَامًّا عَلَى نَبِي تَنْحَلُّ بِه العُقَدُ ، وَتَنْفَرِجُ بِه الكُرَبُ، وَتُقْضَى بِه الحَوَائِجُ، وَتُنَالُ بِه الرَّغَائِبُ وَحُسْنُ الخَوَاتِيْم، وَيُسْتَسْقَى الغَمَامُ بِوَجْهِهِ آلكَرِيْم .

ويراك ترضى وتصبر فيرضيك بما تتمنى..