King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

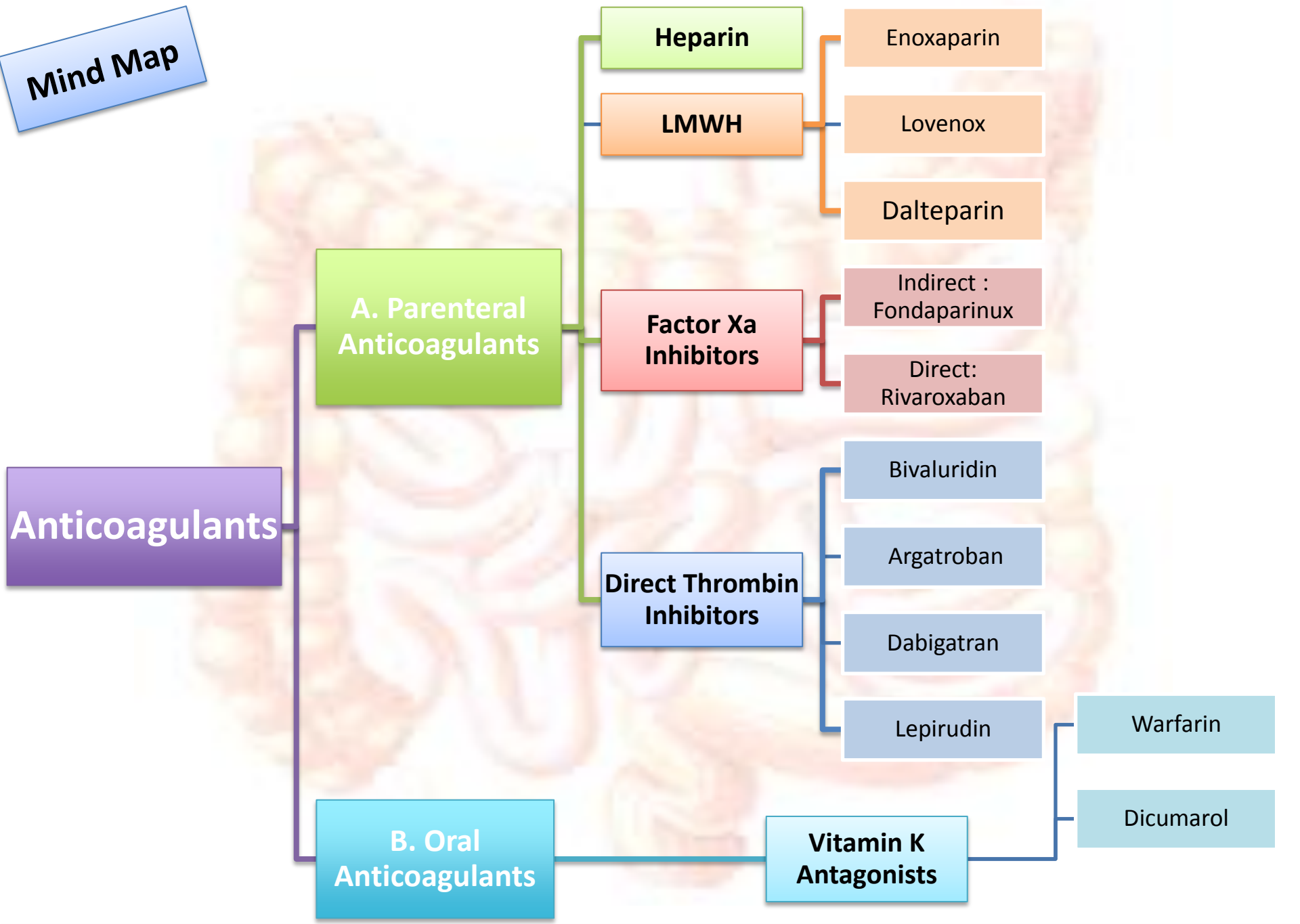
PHARMACOLOGY 433

MED 433 Teams

L8:Anti-coagulants

OBJECTIVES

- ✓ Re-visit the coagulation cascade
- ✓ Classify drugs acting as anticoagulants
- ✓ Elaborate on their mechanism of action, correlating that with methods of monitoring
- ✓ Contrast the limitations & benefits of injectable anticoagulants in clinical settings
- ✓ Emphasis on the limitations of VKAs & on variables altering or modifying their response.
- ✓ Apply such variability in a clinical scenario.



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Introduction
+important

Intrinsic Pathway Clotting: slower / accessed by aPTT *	Extrinsic Pathway Clotting: is rapid in sec. / accessed by PT **
BV Injury ↓ FXII → FXIIa ↓ FXI → FXIa ↓ FIX → FIXa ↓ FVIIIa FX → **FXa**	Tissue Injury ↓ Tissue Factor ↓ FVII → FVIIa ↓ FX → **FXa**

Common Pathway

FXa , Va, Ca++
↓
Prothrombin → Thrombin IIa
↓
Fibrinogen → Fibrin monomer (soluble)
↓ FXIIIa
Fibrin polymer (Insoluble)

FXII : factor XII FXIIa : factor XII , active form
*aPTT = Activated Partial Thromboplastin Time
**PT = prothrombin time

Intrinsic Pathway

1. The trigger is the activation of factor XII by injured blood vessel.
2. Activate factor (XIIa) will activate XI to Xla
3. Xla will activate IX to IXa
4. IXa + VIIIa **activate X to Xa**
5. Common pathway

Extrinsic Pathway

1. Triggered by material released from damaged tissues
2. Tissue Injury activate Tissue Factor
3. Tissue Factor activate VII to VIIa
4. VIIa **activate X to Xa**
5. Common pathway

Common Pathway

1. Xa + Va + Ca is activate prothrombin to thrombin IIa
2. Thrombin act on fibrinogen ? fibrin monomers
3. Factor XIII convert the fibrin monomers to Fibrin polymer

AT III (anti-thrombin III) is normally in body to prevent clotting , work manly at factor X and Thrombin IIa

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ANTICOAGULANTS

>VENOUS THROMBOSIS

Anti-coagulant used more for venous thrombosis
Anti platelet used more for arterial thrombosis

	A. Parenteral Anticoagulants
	1. UF Heparin
Work at	Factors : XIIa, XIa, IXa, **Xa and Thrombin IIa (equal effect)**
M.O.A	Inactivation of Coagulant Factors by Anti-thrombin III (the heparin active the Anti-thrombin III 1000 time than normal)
Pharmacokinetic	1. Rapid / Variable 2. 3000-30000 *molecular weigh 3. Work at Thrombin IIa and Xa equally 4. No effect on fibrin-bound IIa (not close all thrombus = still have active site) ➔ Re-thrombosis ➔ need monitor 5. Low bioavailability ➔ binds to plasma proteins, endothelium & macrophages
Monitor by	aPTT (Activated Partial Thromboplastin Time) (1.5 - 2.5 times normal [30sec]) Or CT (clotting time) (2-3 times normal [5-7 min)
Antidote	Protamine Sulphate IV +/ Fresh blood (give in if drags causes bleeding)
Adverse effects	1. Heparin Induced Thrombocytopenia (HIT) (Sensitive to PF4) 2. No predictable anticoagulant effects (in hospital setting, repeated monitoring) inter-patient & intra-patient variability in response to a given dosage 3. Re-thrombosis ➔ because heparin activates platelets & it does not neutralize fibrin-bound II a

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Heparin Induced Thrombocytopenia (HIT)

- in 4% patient on heparin , latency 5-10 dys, Venous > Arterial thombosis
- after 1st exposure or 2-3 dys. after re-exposures (Because heparin is Sensitive to PF4 (platelet factor 4) , causes immune action in 2nd exposure)
- Causes : **Thrombocytopenia (↓** platelets count) **+ thrombosis**

Management : Heparin discontinuation + Give ➔ DTIs

No packed platelets ➔ More thrombosis

No warfarin ➔ ppt .venous gangrene

Heparin Induced Thrombocytopenia → Thrombosis + ↓Platelet count

The difference between Re-thrombosis and Heparin Induced Thrombocytopenia

Heparin Induced Thrombocytopenia
is caused by the formation of abnormal antibody that activate platelets. If someone receiving heparin

Patient may develop heparin Induced Thrombocytopenia (HIT) **within 7 -10 days**

Patient may develop Re-thrombosis **within 1-2 days** after exposure to heparin)
→ activates platelets & it does not neutralize fibrin-bound II a

The treatment for this case is
Direct thrombin inhibitors

Different between thrombosis causes by heparin : if due to HIT : 5-10 days after take heparin , with Thrombocytopenia
If due to re-thrombosis : 2-3 days after take heparin , without Thrombocytopenia

ANTICOAGULANTS

>VENOUS THROMBOSIS

A. Parenteral Anticoagulants	
	2. LMWH (lower molecular weight heparin)
	Enoxaparin, Lovenox, Dalteparin
Work at	> Factor Xa
M.O.A	Inactivation of Coagulant Factors by Anti-thrombin III (the heparin active the Anti-thrombin III 1000 time than normal)
Pharmacokinetic	1. < 8000 *molecular weigh 2. No effect on fibrin-bound IIa 3. No effect on Thrombin Iia 4. Greater inhibition of thrombin generation 5. ↑ Bioavailability; as it hardly binds to plasma proteins, endothelium & macrophages
Monitor by	Plasma and Factor Xa
Advantage	1. **↓Incidence of thrombocytopenia; as it resistant to PF4** = rare Heparin Induced Thrombocytopenia 2. **↓Incidence of bleeding tendency** (↓ effect AT III & ↓ platelet interactions) 3. **↑ Predictability of anticoagulant response** (little inter-patient and intra-patient variability in response to a given dosage. So → effective anticoagulant activity can be achieved by calculating dosages based on body weight without the need for laboratory monitoring) 4. **Much better tolerability** : given subcutaneous (↓ frequency of administration due to longer duration of actio and ↓ need for regular monitorin , Outside hospital settings)

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ANTICOAGULANTS

>VENOUS THROMBOSIS

A. Parenteral Anticoagulants		
	3. Factor Xa Inhibitors	**4. Direct Thrombin Inhibitors**
	Indirect : Fondaparinux Direct: Rivaroxaban (oral)	Bivaluridin, Lepirudin, Argatroban Dabigatran (oral)
Work at	Factor Xa only	Thrombin Iia (No effect on Xa)
M.O.A	Inactivation of Coagulant Factors by Anti-thrombin III (the heparin active the Anti-thrombin III 1000 time than normal)	
Pharmacokinetic	1. Pentasaccharide 2. No effect on fibrin-bound IIa	effect on fibrin-bound IIa
Monitor by	Plasma and Factor Xa	aPTT

Treatment of pregnant women

1-UF Heparin *can be used*

2-LMWH (lower molecular weight heparin) *can be used*

3-warfarin *can't be used*

ANTICOAGULANTS

>VENOUS THROMBOSIS

	B. Oral Anticoagulants
	Vitamin K Antagonists
	Coumarins ; **Warfarin , Dicumarol**
Work at	Factors : II, VII, IX & X
M.O.A	Decrease Synthesis Of of Coagulant Factors
Pharmaco kinetic	1. Slow / Latency / Variable 2. Warfarin > 40 times potency than Dicumarol 3. Needs de novo synthesis
Monitor by	PT (2 times) INR (normal = 2.5)
Antidote	Vit. K_1 infusion +/ Fresh blood

INR (international normalised ratio) : is a laboratory measurement of how long takes blood to clot,
It used to determine the effect of oral anticoagulant.
↑INR → Bleeding
↓INR → Thrombosis

other Oral Anticoagulants
1- Rivaroxaban (Factor Xa Is)
2- Dabigatran (Direct Thrombin Is)

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Vit. K antagonist (warfarin)

MOA	Precursors of factors II, VII, IX & X require carboxylation of their glutamic acid residues to allow them to bind to phospholipid surfaces. This is provided by Vit. K as it changes from its oxidized to its reduced form. Instantaneously , the reduced Vit K has to recycle back to oxidized form by Vit K epoxide reductase. This enzyme is blocked by VKAs ➔ losing the coagulation factors the ability to function.
limitation	✓ Wide variation in drug response ➔ a necessity for continuous monitoring (PT) & dose adjustment . ✓ Has narrow therapeutic window: high plasma binding protein , so action depends on very small fraction of free drug. So any change in its level can be hazardous. ✓ Slow onset of action, so not in given in emergency conditions ✓ Has latency in its action➔ presents the time needed to launch new biologically inactive coagulation factors ✓ Common genetic polymorphisms in CYT P450 isoforms that metabolizes warfarin ➔ adds to its non predictable response ➔ liability to toxicities or under use. ✓ Numerous food- & drug-drug interactions ➔ liability to toxicities or under use. ✓ **Contraindicated in pregnancy** ➔ give heparin or LMWH instead

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*Factors altering response to vit.K antagonist:

*dr.omnia said this slide is just for your information

Increase response:

1-Vitamin K deficiency:

a- Inadequate diet; malnutrition, dieting.

b- Inadequate absorption; diseases of small intestine, diseases ↓biliary secretion.

2-Impaired synthesis of clotting factors:

a- In hepatocellular disorders :(hepatitis; viral, autoimmune, drug-induced, chronic alcoholism).

b- In hepatic congestion; in congestive HF).

3-Increased catabolism of clotting factors:

In hypermetabolic states; as in fever, thyrotoxicosis.

Decrease response:

1- Decreased plasma protein binding:

↑elimination of free drug & shortening of its t1/2 as pts with nephrotic syndrome (proteinuria).

2-Decreased catabolism of clotting factors:

Hypothyroidism.

3-Hereditary resistance to oral anticoagulants.

*Drugs modulating response to vit.k antagonists:

*while this part is so important

↑INR: Bleeding

oral antibiotics: decrease vit. K synthesis.

liquid paraffin: inhibition of vit k absorption.

chloramphenicol, & cimetidine: microsomal enzyme inhibitor →prolonged action.

phenylbutazone & salicylates: displacment of the drug from protein binding sites.

NSAIDs and heparin:↑bleeding tendency.

↓INR: Thrombosis

cholystyramine, colestipol: Inhibition of drug absorption

Vit K, oral contraceptives:↑synthesis of clotting factors

carbamazepine, rifampicin: microsomal enzyme inducer →decreased action.

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IMPORTANT

SCENARIO

An old, peptic ulcer patient, sustained on cimetidine, has been bed ridden since a month following a major orthopedic surgery for pelvic fracture. The last week he began to complain of pain, tenderness, warmth & swelling of his left leg. He was diagnosed as deep vein thrombosis. His treating physician put him first on heparin that was replaced after three days by VKAs. Today he began to show bleeding of gums.

What is the expected explanation of his finding?

Warfarin toxicity → because of the enzyme inhibitor **cimetidine**

Will the treating physician 1st of all, consider giving an antidote to stop bleeding (if so then state) or will he probably ask for lab investigation (if so then state)?

bleeding of gums→not emergency situation ,so we have time to do lab investigations

Once lab findings are there, is the physician expected first to withdraw or to adjust the existing therapy?

Give him other than cimetidine

IMPORTANT

A young rheumatic artheritic patient has underwent valve replacement and is sustained on warfarin therapy for the last three years. When she married, last summer, she did not want to get pregnant, so she has taken since then, oral contraceptive pills. Her regular lab monitoring today showed a decrease in INR this time.

What is the expected explanation of her lab result?

contraceptive induce the coagulation factors → ↓INR →tendency of thrombus

What will the treating physician consider doing?

-Giving heparin on top

-Adjusting warfarin dose → The first step

- Stopping the OC → better

- Stopping warfarin

A 53 years old patient had an aortic valve replacement since 5 years and he is sustained on warfarin. A week ago, he developed low grade fever, diarrhea and was diagnosed as having typhoid. He was given rehydration fluid and a course of chloramphenicol.
Today he is complaining from haematuria.

Which one of the following best explains the haematuria?

- Inhibition of Vit K synthesis by chloramphenicol
- Displacement of warfarin from protein binding site by rehydration
- Decrease in warfarin metabolism induced by chloramphenicol
- Inhibition of Vit K absorption caused by the diarrhea

Which is the right decision to do in such a case?

- Give a urinary antiseptic for fear of infection
- Stop administering the regular intake of warfarin
- Adjust the dose of warfarin after monitoring the situation.
- Stop the course of chloramphenicol intended for typhoid therapy

summary

	Parenteral Anticoagulant *(Used in acute 'emergency' Cases)*				Oral Anticoagulants
	Unfractionated heparin	**LMW Heparin**	**Direct Thrombin inhibitors**	**Factor Xa Inhibitor**	**Vitamin K antagonist**
Molecule weight	3000-30000	< 8000		Pentsaccharides	
Acts on	XIIa, XIa, IXa, Xa, IIa And thrombin *(1000 more potent than Anti thrombin3)* *LMWH:* **Works more on Xa**		Thrombin 2a	Factor Xa	Factors II, VII, IX &X
Drugs	Heparin	Enoxaparin Lovenox Dalteparin	**Reversible:** • Bivaluridin • Argatroban • Dabigatran **Irreversible:** • Lepirudin Irreversible is more dangerous	**Indirect:** Fondaparinux **Direct:** Rivaroxaban **Which is taken Orally**	**Coumarins:** • **Warfarin** > 40 times potency than: • Dicumarol
MOA	**Inactivation of Coagulation Factors by Anti-thrombin III**				**Decrease Synthesis**
Pharmaco kinetics	• **Rapid** • **Variable** *(unpredictable)*				• **Slow** • **Latency** • **Variable**
Monitor	• **aPTT** (1.5 - 2.5 times normal [30sec]) • **CT** (2-3 times normal [5-7 min])				• **PT** (2 times) • **INR** (2.5)
Antidote	• **Protamine Sulphate IV** ➔ 1mg for each 100 units UFH • **Fresh blood**				• **Vitamin K1 infusion** • **Fresh blood** • Needs de novo Synthesis

Quiz yourself

Answers 1.C 2.C 3.C 4.B 5.C 6.B 7.C 8.A 9. B

1. The primary advantage of enoxaparin over heparin is that it:
   a. more effectively Inhibits the synthesis of clotting factors
   b. does not case thrombocytopenia
   c. has a longer half-life

2. Which one of these drugs is a direct thrombin inhibitor:

   A. Enoxaparin
   B. Rivaroxaban
   C. Lepirudin

3. Which one of these drugs is a Pentsaccharides:
   A. Heparin
   B. Dalteparin
   C. Fondaparinux

4. Pregnant lady has deep vein thrombosis , she has to take anticoagulant.. Which drug is safe to her?

   A. Warfarin
   B. Heparin/LMWH
   C. NSAIDS

5. The MOA of Vitamin K antagonist is:

   A. Inactivation of Thrombin 2a
   B. Inhibition of Factor Xa
   C. Decrease Synthesis

6. A patent is given heparin then after 2 days rethrombosis occurred, Which drug can properly monitor his situation?
   A. Low molecular weight heparin
   B. Direct thrombin inhibitors
   C. Factor X inhibitor

7. 80 years patient has Myocardial infarction, he cant go to the hospital .. Which drug is more effective and suitable for his situation ?
   A. Heparin
   B. Warfarin
   C. LMWH

8. Which drug is contraindicated for pregnant lady with Venous thrombosis?
   A. Warfarin
   B. Heparin
   C. LMWH

9. Which one of these drugs works more on Xa:

   A. Heparin
   B. Enoxaparin
   C. Warfarin

Done by

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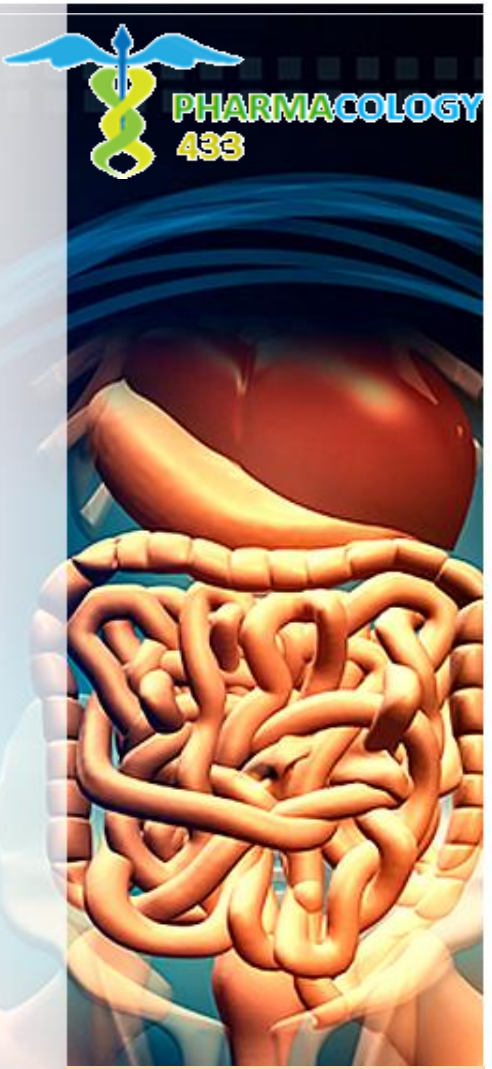
It always seems impossible until it is done

BEST OF LUCK



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