PHARMACOLOGY

TEAM 432

Cytochrome system and drug metabolism

Objectives

1)Revise the intent of drug metabolism and its different phases
2)Define the role of cytochrome system in relation to drug metabolism
3)Expand on the nature, location, nomenclature, structure, distribution & function of CYT P450
4)Focus on its regulation; directly & indirectly, its induction & inhibition in relevance to drug interactions
5)Interpret the molecular mechanism of interactions by CYT P45
6)Classify its different isoforms, their substrates, inducers & inhibitors
7)Delineate some of its genetic variations

This work is based on what dr Omnia focused on and some important info,, Cases and questions are those which are mentioned during the lecture

Color Guide

Slides = Black
Females notes= Green
Female slides=purple
Males slides= Blue
Explanation=Orange

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introduction

5000 function?

Drug metabolism and break down?

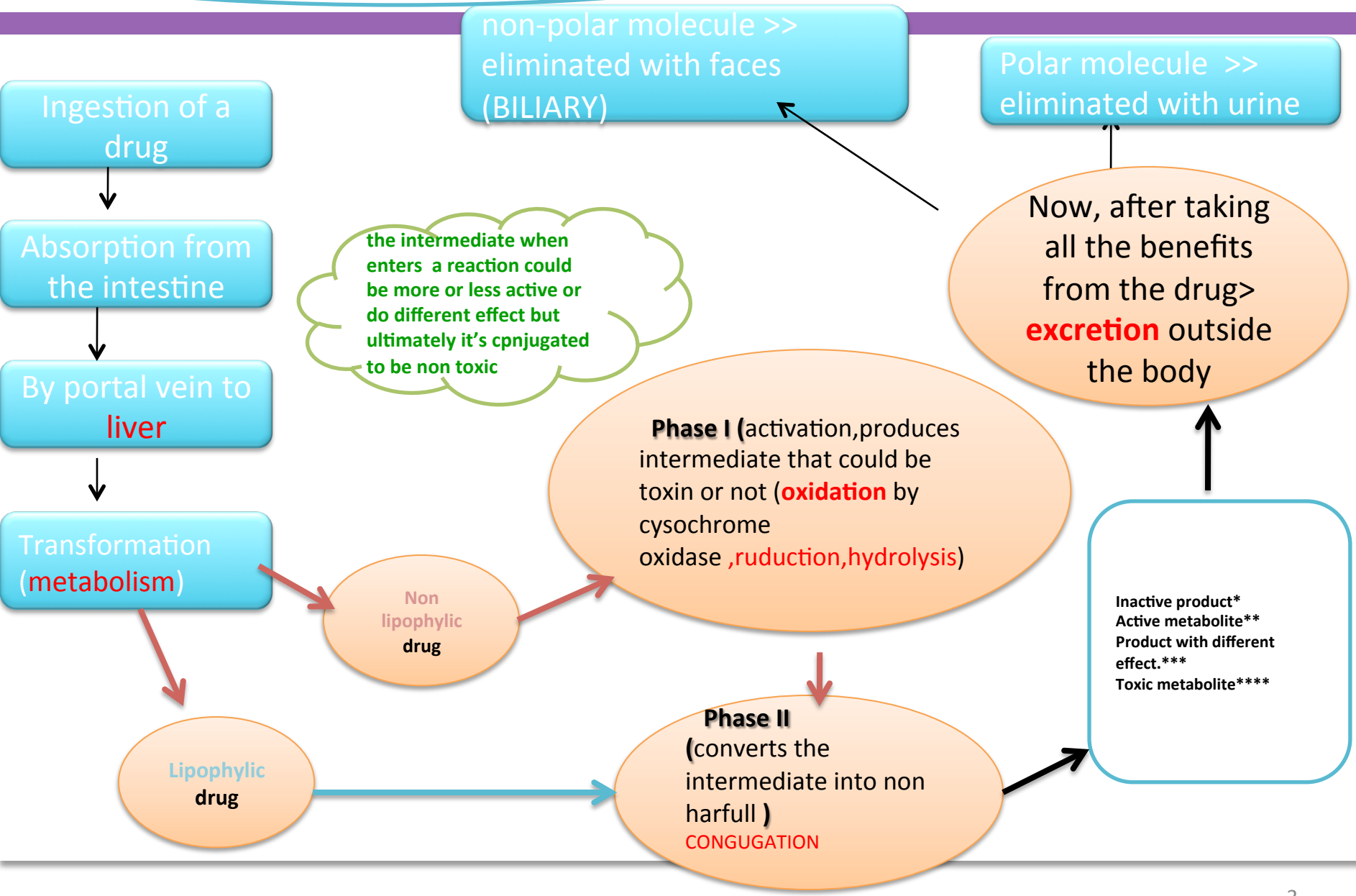
"METABOLIC CLEARING HOUSE"

First pass metabolism ?

Converts substances into excreted forms?

I do all these jobs

Drugs' pathways



Cyrochrome system ?

Its key enzymes are part of a cascade➔ shuttles electrons from molecular oxygen to oxidize the drugs

‘ Cytochrome P450“, CYT 450 superfamily is the terminal rate limiting oxidase of this system

*attached to SER of hepatocytes.

Cytochrome means colored cells

They color the liver cells dark red as they contain iron ⟶ rate limiting controlling all the cascade

*"P450“ absorbs a wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

*They are isolated in the subcellular fraction termed the MICROSOMES

➔ Liver microsomal enzymes

STRUCTURE

They are heme-containing isoenzymes (proteins)

DISTRIBUTION

Highly concentrated in hepatocytes

Enterocytes of the small intestine present their principal extra-hepatic source

Very small quantities in kidneys, lungs, & brain.

Function

Responsible for most of the **OXIDATIVE METABOLISM** of:

1)Endogenous substances: steroid hormones, prostaglandins,lipids, & fatty acids

2) compounds: diet(food & beverages) / Drugs/ environmental xenobiotics

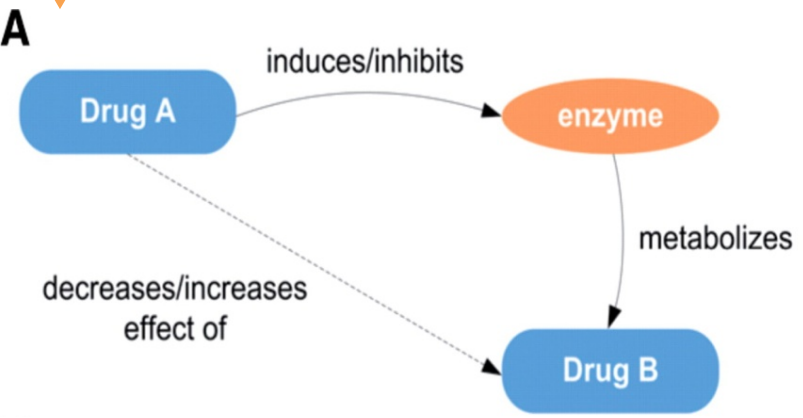
→ Metabolizes the substrate(which the enzymes will work on)

Regulation

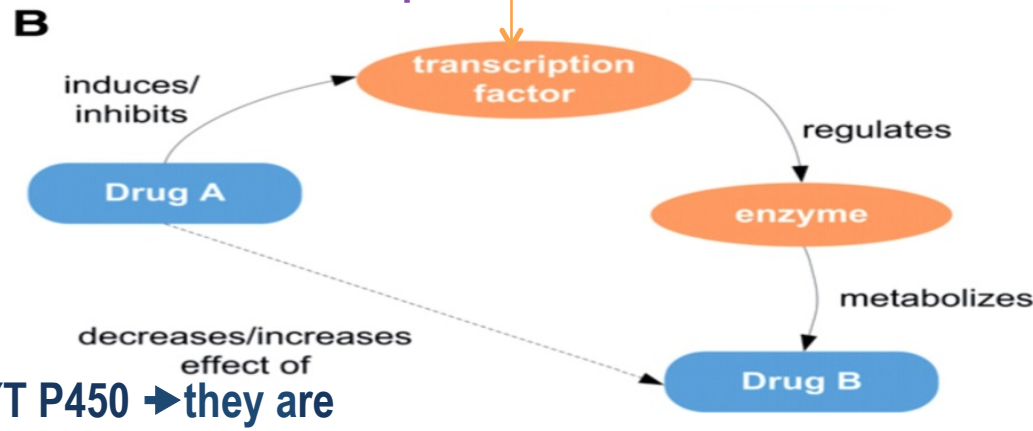
Drugs could be inducer, inhibitor or non of them

Activation or **Inactivation** (processed be any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophylic) that have to be Metabolized) of the CYT P450 can be achieved either

Directly : on the enzyme itself(activation or inhibition)



Indirectly by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors

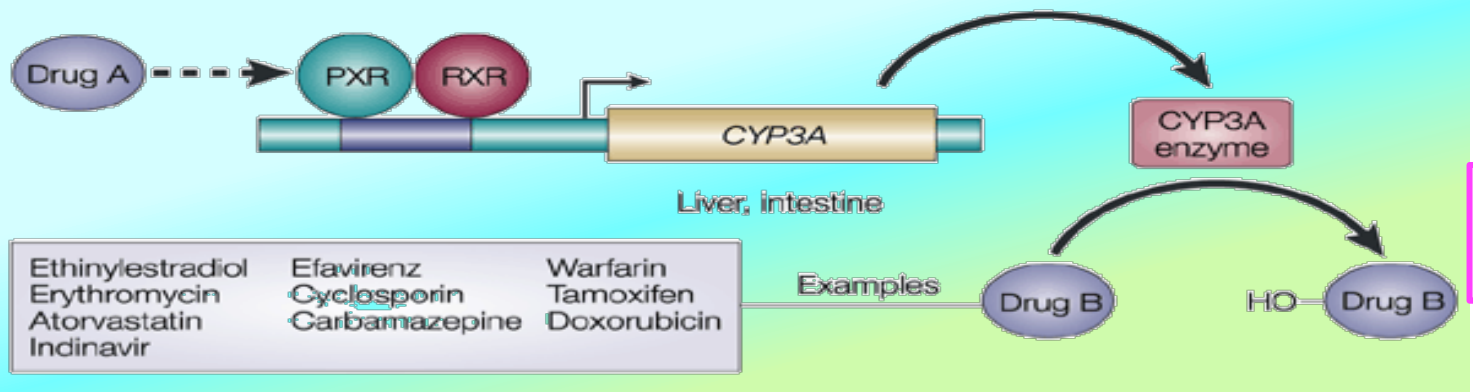


When **drugs** play a role in regulation of the CYT P450 ➔ they are termed

- Enzyme Inducers if Activate the enzyme
- Enzyme Inhibitors if Inactivate the enzyme

Pharmakokinetics of Drug-drug interaction

Molecular Basis Of Drug–drug Interaction



Drugs are inducers, inhibitors or have no effect

The orphan nuclear receptor **PXR** is a **TRANSCRIPTION FACTOR** (*to increase or decrees production of cytochrome enzymes*). that regulates the expression of the *CYP P450 genes*

If Drug A is INDUCER → it binds & activates **PXR** → which translocates in nucleus→ dimerize with **RXR** → the heterodiamer **PXR / RXR** will induce **EXPRESSION** of CYT P450 isoenzymes to →↑metabolism of Drug B(↑in its own metabolism → ↓its pharmacological action (*Tolerance or complete nullification*) *and*↑ in metabolism of co-administered)

Net result ↓ EFFICACY

If Drug A is an INHIBITOR, its binding will prevent activation → **REPRESSION** of CYT P450 isoenzymes to →↓metabolism of Drug B (↓/ retard its own metabolism & excretion and also that of its co-administered drugs.then↑ / prolong its action & that of its co-administered drugs.)

Net result ↑TOXCICITY

PXR, pregnane X receptor
RXR, retinoid X receptor.

Classification

CYT P450 has been classified into
1) Families designated by Numbers
2) sub families designated by Letters

CYT P450 ➔Major Contributor to Phase I Metabolism
*most important one in drug metabolism is CYTP3A4

Present in high quantities so more effect in metabolizing drugs

Each enzyme works on specific drug to induce or inhibit its metabolism

Cytochrome P450 Isoforms

- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

CYT P450 3A4

VERY IMPORTANT TABLE!

Substrates	Inhibitors	Inducers
Immunosuppressants	Protease Inhibitors	Rifampicin
* Cyclosporine	Ritonavir	
Azole Antifungals		Phenytoin
* Fluconazole	Cimetidine	Carbamazepine
Antibiotics	Chloramphenicol	Barbiturates
*Erythromycin, Clarithromycin	Nefazadone	
Ca channel blockers		Dexamethazone
Amlodepine, Verapamil	Grape Fruits	Progestins
Statins; Atorvastatin		
Antiarrhythmic; Amidarone		
Cancer Chemotherapy:		
Cyclophosphamide, Tamoxifen		
Non-Sedating Antihistaminics		
Astamizole		
Benzodiazipines		
Midazolam, Clonazepam		

*They are inhibitors and could be induced or inhibited

N.B In this slide you need to know the following :

- CYT P450 iso-form 3A4 is most abundant form and most common one for metabolizing the drugs
- Any thing it metabolizes is a substrate but here we separated them into (inhibitors / inducers) to show you that some of the substrates have an action on the enzyme that will affect the outcome (metabolism) of the co-administered drugs which is in this table written (substrate) (eg. say you give a patient fluconazole for some fungal infection at the same time it was co –administered with phenytoin to treat the patient's epilepsy what will happen ? You must think in this order → both drugs are substrates of the enzyme however the 2nd drug has an inducing effect on the enzyme →which in turn facilitates the metabolism of the 1st drug → decreasing its efficacy in treating the fungal infection) apply this in all other forms
- ***You must memorize all the drugs written in this table***
- **Erythromycin Clarithromycin Fluconazole Cyclosporine are very prominent enzyme inhibitors on there own and they are also inhibitors of the metabolism of the other drugs if they were co-administrated with them. meaning if they were prescribed alone they inhibit their own metabolism and prolong their action , but still if you co-admit them with either one of the inducers or inhibitors their metabolism will be affected.**

An example on CYT P450 3A4 and the drug to drugs interaction the following MCQ'S

A 50 years old, patient was treated for the last 3 years by the hypocholestrolemic agent***; atorvastatin***. Yesterday he began to complain of severe muscle pains, weakness and reddish discoloration of urine He receives daily multivitamins and his lab results last week, proved that he has become diabetic, for which he was prescribed metformin. He was also started on a course of ***fluconazole*** for a concomitant fungal infection. From drug history, the diagnosis of his current state was likely rhabdo-myositis (severe muscloskeletal toxicity) and was verified by the lab finding of severe elevation in creatinine phosphokinase. "

Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state

A. **Metformin + Atrovastatin**
B. **Atrovastatin + Fluconazole**
C. **Metformin + Fluconazole**
D. **Fluconazole+ Multivitamins**

Atorvastatin is the substrate of CYTP450 (3A4) that was affected by fluconazole which is also a substrate but with an inhibitory effect on the enzyme and so increasing the ADR produced by atorvastatin

TIP FOR ANSWERING : doctor said ignore all the list of drugs that were mentioned in the question and only look for the ones that were in the table because these are the one s that will have the drug to drug interaction

Which one of the following is the enzyme inhibitor ?

A. **atorvastatin**
B. **multivitamins**
C. **fluconazole**
D. **Metformin**

Simply because you have to memorize that it is an enzyme inhibitor

Which on the following will not be metabolized and will have a prolonged duration of action ?

A. **atorvastatin**
B. **multivitamins**
C. **fluconazole**
D. **Metformin**

2ndry to the inhibitory effect of fluconazole's on the enzyme (drug to drug interaction) atorvastatin wont be metabolized increasing its duration of action and producing the adverse effect

e.g A and B patients are taking the same dose of a drug.
A has toxicity while B doesn't
In Genetic variation toxicity within the therapeutic dose

Genetic Variation

are the reasons behind the ALTERED RESPONSE to drug therapy from patient to another.

CYP2D6 has the most frequent polymorphisms in all CYT P450

When polymorphism occurs ➔ ↓ metabolizing capacity of CYP2D6

i.e those who exhibit the polymorphism become poor metabolizers

1)Metabolism of some drugs neuroleptics, tricyclic antidepressants, antianginals agent (perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed ➔ so side effects & toxicity develop. i.e.

*Neuropathy after therapeutic doses of perihexiline

*Severe brady arrhythmias ➔ heart block on therapeutic dose of propafenone or metoprolol

2) The pro-drugs cannot be converted to their therapeutically active metabolite (so lowering the efficacy of the drug of this prodrug); e.g poor analgesia with codeine & tramadole (in tooth extraction or minor surgeries if it's not activated pain persist because they are not transformed into active forms

CYP2C9.

Warfarin, phenytoin, & tolbutamide are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.

Clearance of these drugs is impaired in genetic variation of the enzyme(increase toxicity)

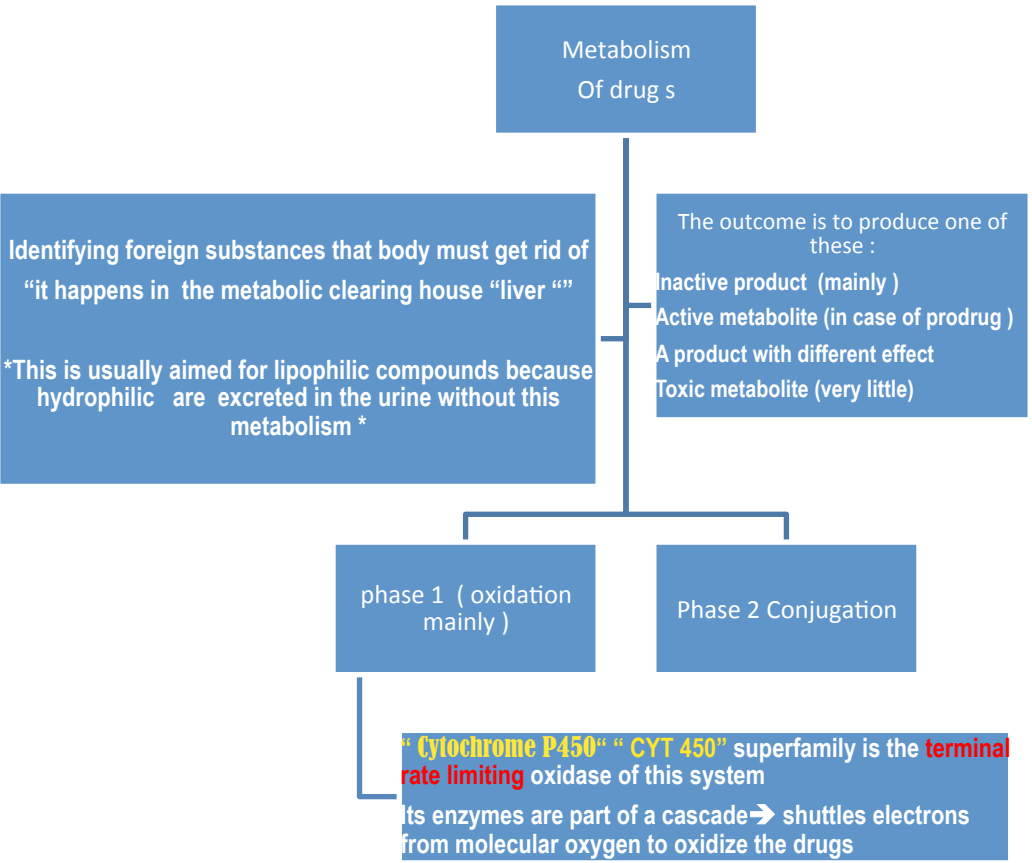
CYP2C19

Polymorphism in CYP2C19 showes increased & prolonged action of its substrates as omeprazole

This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with He*licobacter pylori*

Summery

A- CYT P450 GENERAL FEATURES AND REGULATION:



CYTP450:

Is mainly found in the liver's SER ,subcellular structure termed the MICROSOMES→ Liver microsomal enzymes and contains iron

- Its Main function **OXIDATIVE METABOLISM of substrates that are endogenous or exogenous(drugs)**
- its ***regulated*** :

A- directly : drug (A) acts on the enzyme directly by either inducing/inhibiting its action → affects drug (B) which will either have and increase/decrease in its effect

B- indirectly: when the drug (A) acts on a genetic level by inducing/inhibiting the action TRANSCRIPTION FACTOR PXR(most important factor for the enzyme) → which will suppress/express the enzyme synthesis →which in turn will influence drug B's activity increase/ decrease

- Has multiple isoforms most important are :

1. CYP2D6
2. CYP2C9.
3. CYP2C19
4. CYP1A2
5. CYP3A4

Summery

Some hydrophilic drugs don't need to be metabolized By the liver >execrated directly by the kidney

B-Outcome Of Drug-drug Interactions Mediated By CYT P450

-The most important isoform in this process is *3A4*

-IN RELATION TO ENZYME INDUCERS of their own metabolism or other drug the nets effect is →decrease in the efficacy

-IN RELATION TO ENZYME INHIBITORS of their own metabolism or other drug the nets effect is →increase toxicity

- **If the drug was inducing/inhibiting a certain iso form of CYT SYSTEM it can only influence other drugs with the same isoform but not different iso forms (meaning if drug A works on 3A4 It will only affect drug B that is acted upon by 3A4 and wont have an affect on drug B that is metabolized by another form say 2D6)**

-TIP FOR MCQ there will 2 drugs (from the ones you will memorize from the table above)amongst multiple mentioned in the scenario these are the one that will interact so always choose them and then decide whether one was an inducer or not and finally what its affect is on the other drug

C-Genetic Variation

- ***CYP2D6*** **isoenzyme has the most frequent polymorphisms in all CYT P450 by which it will result in : Increase toxicity of eg. tricyclic antidepressants or decrease in the efficacy if taken in prodrug form eg. tramadol**
- Other isoform involved in genetic variation are :

1. CYP2C9 eg. warfrin
2. ***CYP2C19*** (the beneficial type) meaning if the patient a has a polymorphism in it and developed a peptic ulcer the omeprazole therapy which wont be metabolized in this case will facilitated the faster healing and response to therapy

- Tip for the MCQ there will be only one drug and mentioned and its going to say therapeutic / prescription/regular dose this will help you know she if referring to genetic variation problems

MCQ'S

If a patient was known to have arrhythmic problems and was put on Amidarone later on how ever he became infected with TB and was put on Rifampicin he also known to have daily multivitamins uptake

Q1- which one of the following would you suspect to see a decrease in its efficacy ?

A. Amidarone
B. Rifampicin
C. Multivitamins

Q2- based on Q1 who was responsible in inducing **CYT 3A4 's** activity ?

A. Amidarone
B. Rifampicin
C. Multivitamins

Q3- If an angina patient was put on a therapeutic dose of perihexiline and there after he develops Neuropathy What's the most likely cause ?

A. drug to drug interaction
B. ↓ metabolizing capacity of CYP2D6 due to polymorphism and increase in toxicity
C. narrow therapeutic index

Q4- if a patient had a tooth extraction and was put on tramadol however it turns to have no relieving effect this is due to ?

A. Increased toxicity because CYP2D6 polymorphism
B. Increased efficacy due to CYP2D6 polymorphism as the drug is taken as prodrug and metabolized
C. Decreased efficacy due to CYP2D6 polymorphism as the drug is taken as prodrug and not metabolized
D. Decreased efficacy due to CYP3A4 polymorphism as the drug is taken as prodrug and not metabolized

Ans
1-A
2-B
3-B
4-C

PHARMACOLOGY

TEAM 432

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