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Review Article

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THE EFFECT OF ENZYME INDUCTION AND ENZYME INHIBITION ON THE TOXICITY AND EFFICACY OF THE PRESCRIBED DRUGS- A REVIEW

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ABSTRACT

The development of the novel therapeutic agents or drugs will be widely affected by Parameters related to the chemistry (structure activity relationship), Pharmacology (mechanism of action of the drug) and the Pharmacokinetic profile of the drug (metabolism characteristics) will play an important role. Before a drug is newly launched in the market various pre clinical studies has to be undertaken to determine the efficacy, toxicological and the pharmacokinetic profile of the drug. In the clinical studies where the drugs has to be tested on the living beings, much concentration has been done on the safety profile of the drug which is the only defined factor for its approval and use in the market.

KEY WORDS

Enzyme Induction, Enzyme inhibition, Metabolism, Drug inhibition.

INTRODUCTION

The biological response of the human body to the drug is dependent on the complex network of factors as illustrated in **Fig. (1)** [1]

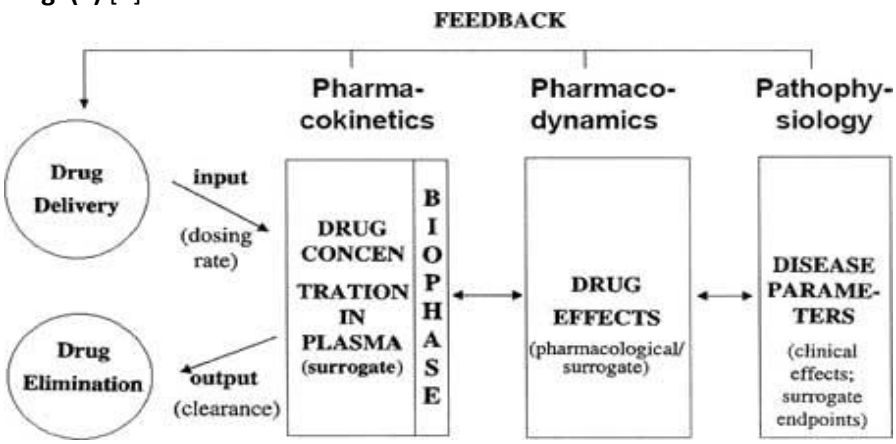

Figure 1: Schematic illustration of the complex interrelationships of the factors that influence drug response [1].

Drug metabolism is an important tool of biochemical pharmacology [2]. The drug's pharmacological activity is nullified by these processes which involve enzymes in the hepatocytes and the gut wall. Thus metabolism being a main tool by which a therapeutic drug gets inactivated [2].

Metabolism being a process wherein the living organisms effect the change in the molecule, such process involving transformation of drug from one form to another is called biotransformation of drug

Metabolism converts lipophilic forms of drugs to the polar metabolites thus reducing its ability to get reabsorbed in the kidney tubules and fasten its excretion in the urine [2].

Implications ought for this metabolism being the drug- drug interactions, carcinogenesis, bio activation, substrate inhibition, enzyme induction as well as termination of drug action.

2. Drug- Drug interactions:

2.1. Pharmacokinetic Interactions

This is when one drug affects the availability (absorption), distribution, metabolism or excretion of another drug [3, 4]. A change in blood concentration causes a change in the drug's effect [3, 4].

2.2. Pharmacodynamic interactions

These interactions are due to competition at receptor sites or activity of the interacting drugs on the same physiological system [3, 4]. There is no change in the plasma concentrations of interacting drugs [3, 4].

2.3. Pharmaceutical Interactions

These can be classified as those interactions that occur prior to systemic administration. For example incompatibility between two drugs mixed in an IV fluid [4]. These interactions can be physical (e.g. with a visible precipitate) or chemical with no visible sign of a problem [4].

Many of the pharmacokinetic reactions involve metabolism, reactions involving microsomal enzyme system the most active being the cytochrome (CYP) 450 family of enzymes of which only few are responsible for the maximal metabolic reactions involving drugs [5].

The Cytochrome P450 enzyme system is one of the important enzyme systems to deal with the lipid soluble environmental chemicals [5]. In the future aspects of this cytochrome system importance of it in metabolizing lipid soluble drugs has been recognized [5]. The cytochrome P450 performs the function either by oxidizing, reducing or hydrolyzing the drugs and this allows other group of enzymes called as conjugation enzymes to attach polar group moieties to the drug making it more water soluble and excreted in the urine [5].

The CYP enzymes are present primarily in the endoplasmic reticulum of the hepatocytes in the liver which is the main site of metabolism for the drug, and small quantities present in kidneys, lungs and brain [6]. However isoenzymes are found in many tissues and CYP3A4 in the mucosa of small intestine. CYPs involv in gut are responsible for various drug interactions [7].

3. Nomenclature: The nomenclature follows three- tier classification wherein the isoenzymes with greater than 40% genetic sequence similarity are grouped into families denoted by CYP, and a number e.g. CYP2 , isoenzymes within a family that have greater than 55% sequence similarity are grouped in a sub family designated by a capital letter e.g. CYP2D and Individual isoenzymes that have been specifically identified are given a further number e.g. CYP2D6 [6].

The naming of Cytochrome P450 includes the root symbol "CYP" for humans, an Arabic numeral which denotes CYP family (e.g. CYP2), letters A, B, C including subfamily (e.g. CYP3A) and another Arabic numeral representing the individual gene/isoenzyme/isoform[6].

The Cytochrome P450 gene family have around 60-100 different genes involved in the various chemical transformations [3]. It has been found that only six isoenzymes from the families of CYP1, 2 and 3 are actively involved in the hepatic metabolism [3]. The most important CYP450 isoenzyme is CYP3A4 which is responsible for

50% of drug metabolism followed by it is CYP2D6 controlling 20% and CYP2C9 and CYP2C19 together controlling 15% [3]. The remaining carried out by CYP2E1, CYP2A6 and CYP1A2 [3]. The genes for CYP2D6, CYP2C9, CYP2C19 and CYP2A6 are functionally polymorphic [3]. Therefore approximately 40% of human P450 dependent drug metabolism is carried out by polymorphic enzymes [3].

4. Genetic Polymorphism

The major characteristic for the CYP enzymes is their exhibition of interindividual variation in the expression of the enzyme protein[3]. Genetic polymorphism with clinical implications has been described for 2D6, 2C19, 2C9, 1A2, 3A4 [8, 9, 10]. Polymorphism is defined as existence of two genetically similar identical forms in a population of substantial frequency [11]. A polymorphic gene is one whose frequency is less than 0.99 [11]. Polymorphism in the drug metabolizing enzymes is caused due to mutations in genes that code for specific biotransformation enzyme [11].

Individuals with normal metabolic enzyme activities are often called extensive metabolisers (EM) [12]. Ultra-rapid metabolism (CYP2D6*2xN) is caused by multiple functional CYP2D6 genes, causing an increased amount of CYP2D6 to be expressed [12]. Gene duplication or sometimes multiplication leads to the ultra-rapid (UR) phenotype [12]. A homozygous combination of non-coding alleles leads to the poor metabolizer (PM) phenotype, whereas heterozygous wild type or combinations of alleles with diminished enzyme activity lead to reduced CYP2D6 activity [12]. The prevalence of CYP2D6 PM phenotype differs per race and is reported to be 5 to 10 % in white populations and 1 to 2% in Orientals [12].This is significant because individuals with a CYP2D6 deficiency cannot convert the drug codeine to its active metabolite (morphine)[12].

4.1. CYP3A4

CYP3A4 is the most common and the CYP3A family is responsible for the metabolism of about 60% of all drugs [13]. As well as being present in the liver there is a significant quantity in the gut mucosa and so this isoenzyme is responsible for the metabolism of some drugs in the gut [14, 15, 16]. There is no evidence that this isoenzyme is polymorphic [17]

Inducers: Phenytoin, Carbamazepine and Rifampicin [14, 15, 16].

Inhibitors: Erythromycin, Itraconazole and Saquinavir [14, 15, 16].

4.2. CYP2D6

About 25% of all drugs used today are substrates for this isoenzyme. It exhibits polymorphism and there are extensive and poor metabolizers [15, 16, 18, 19].

Not inducible.

Inhibitors: Paroxetine, Fluoxetine, Cimetidine, Ritonavir [14, 15, 16].

4.3. CYP1A2

This enzyme metabolizes approximately 15% of all drugs used today. No genetic polymorphism.

Inducers: Cigarettes, Barbecued food [15, 16, 18, 19].

Inhibitors: Cimetidine, Omeprazole, Quinolones (e.g. ciprofloxacin) [20].

4.4. CYP2C Family

This family consists of 2C9, 2C10, 2C19 plus others [3]. These enzymes metabolize a smaller number of drugs, however many of these are involved in clinically significant drug interactions [8, 9, 10]. Genetic polymorphism plays a major role with the CYP2C subfamily [3].

Inducers: Phenobarbitone, Rifampicin, Griseofulvin (2C9) [20]. Phenytoin, Carbamazepine, Rifampicin (2C19) [20].

Inhibitors: Azole antifungals, Cimetidine, Omeprazole (2C9 and 2C19) [20]. Lansoprazole, Fluoxetine (2C19) [20].

Isozyme	Substrates	Inhibitors	Inducers
CYP1A2	Clozapine Cyclobenzaprine Fluvoxamine Imipramine Mexiletine Propranolol Theophylline	Cimetidine Ciprofloxacin Clarithromycin Enoxacin Erythromycin Fluvoxamine Ofloxacine Ticlopidine	Polycyclic Aromatic Hydrocarbons (Cigarette Smoke) TCDD(dioxin)
CYP2C9	Diclofenac, Flurbiprofen, Ibuprofen, Losartan (not telmisartan or candesatan) Naproxen, Phenytoin Piroxicam, Sulfamethoxazole, Tolbutamide, Warfarin	Amiodarone, Fluconazole, Fluoxetine, Isoniazid, Paroxetine, Ticlopidine, Zafirlukast	Phenobarbital, Rifampin
CYP2C19	Amitriptyline, Clomipramine, Ciclophosphamide, Diazepam, Imipramine, Lansoprazole, Nelfinavir, Omeprazole, Phenytoin	Cimetidine, Fluoxetine, Fluvoxamine, Ketoconazole, Lansoprazoel, Omeprazole, Paroxetine, Ticlopidine	Carbamazepine, Norethindrone
CYP2D6	Amitriptyline, Clomipramine, Codeine, Desipamine, Dextromethorphan, Imiporamine, Metoprolol, Nortriptyline, Oxycodone, Paroxetine	Amiodarone, Fluoxetine, Haloperidol, Indinavir, Paroxetine, Quinidine, Ritonavir, Sertraline	Rifampin
CYP2E1	Aceaminophen, Chlorzoxazone, Ethanol, Enflurane, Halothane, Isoflurane	Disulfiram	Chronic Ethanol Isoniazid
CYP3A	Alprazolam, Astemizole, Buspirone, Calcium Chanel Blockers Carbamazepine, Cisapride, Cyclosporine, Protease Inhibitors Lovastatin, Midazolam, Simvastatin,Triazolam	Amiodarone, Cimetidine, Clarithromycine, Erythromycine, Grapefruit Juice, Iraconazole, Ketoconazole	Carbamazepine, Glucocorticoids, Phenytoin, Rifampin Ritonavir

TABLE 1: Cytochrome P450 Enzymes Involved in Drug Metabolism: Substrates, Inducers and Inhibitors [3].

6. ENZYME INHIBITION

Enzyme inhibition refers to the decrease in the metabolic rate of the enzyme activity of the drugs being metabolized by Cytochrome P450 system [21]. The clinical significance of the drug-drug interaction depends on the degree of accumulation of the substrate and therapeutic window of substrate [22]. The metabolism of drugs can be inhibited by various mechanisms such as:

6.1. Competitive inhibition

This type of inhibition occurs when two drugs are co administered together causing an increase in the blood concentrations in the body [21]. Inhibition occurs as a result of competitive binding at the enzymes binding site [21]. The competitive inhibition depends on affinity of the

substrate for the enzyme being inhibited; the concentration of substrate required for inhibition and the half life of the inhibitor drug [21].The onset and offset of enzyme inhibition depends on the half life and time to steady the state of the inhibitor drug [21].

6.2. Non competitive inhibition

This type of inhibition occurs when the metabolite forms a complex with the CYP450 enzyme system thus leads to inactivation [21]. In this type the inhibitor binds to the same enzyme as the drug but the binding site is different, resulting in the conformation change of protein [21]. This degree of inhibition doesn't depend on the substrate concentration [21].

6.3. Uncompetitive inhibition

It is the type of inhibition where the inhibitor binds only to the enzyme forming a complex with the drug [21]. The inhibition becomes more marked with increase in the substrate concentration [21].

7. Drugs that prolong half life or increase serum concentrations of other drugs when administered simultaneously.

Inhibitory drug	Drug inhibited	Increase in	Complication reported
Alcohol	Antipyrine	Half life	
Allopurinol	Antipyrine Bishydroxycoumarin	Half life Half life	
Aminopyrine	Antipyrine	Half life	
Bishydroxycoumarin	Chlorpropamide Tolbutamide Diphenylhydantoin	Half life Half life Half life	Hypoglycaemia Hypoglycaemia Ataxia,nystagmus, vertigo,anorexia
Chloramphenicol	Chlorpropamide Cyclophosphamide	Half life Half life	
Contraceptives	Antipyrine Phenylbutazone	Half life Half life	
Disulfiram	Antipyrine Diphenylhydantoin	Half life Half life	 Ataxia,nystagmus
Isoniazid	Hexobarbital Diphenylhydantoin	Half life Half life	 Ataxia,nystagmus
Phenylbutazone	Diphenylhydantoin Diphenylhydantoin	Half life Half life	 vertigo,anorexia, cerebellar damage

TABLE 2: **Drugs that prolong half life or increase serum concentrations of other drugs when administered simultaneously.** [23]

8. Clinical consequences of drug inhibition:

The most important concern is how fast the inhibitor will cause the drug levels to climb towards toxicity and whether the toxic effects could be treated before a serious injury or death [23].

The best option of prevention is

- Ensuring that the health care professionals do not make mistakes and even if they do, we need to ensure that it is not translated into potentially fatal prescription [23].
- The patient must be informed about the toxic effects of drugs when taken along with inhibitors [23].

8.1. Torsades des pointes

It is caused where a compound prolongs the cardiac ventricular QT interval as described in

the ECG wave analysis as the period elapsed between contraction and relaxation of heart [24]. The recommended treatment is to withdraw the causative agent and administer intravenous magnesium sulphate [24]. If the QT interval increases may lead to ventricular tachycardia, arrhythmia and fibrillation [24]. Drugs which trigger this effect includesAmiodarone, sotalol, procainamide and terfenadine [24]. It is important to avoid the QT interval problems wherein terfenadine can be replace by its active metabolite fexofendine [24].

8.2. Sedative effects

The co administration of inhibitors with drugs such as benzodiazepines and others such as buspirone will potentiate the sedative effects markedly [24]. The azole inhibitors in theorder of severity may alter midazolam clearance: **ketoconazole>itraconazole>fluconazole** [24]. The SSRI's fluoxetine and principal metabolite norfluoxetine are potent inhibitors of midazolam clearance and also inhibitor of 3A4substrate and can be replace by sertraline or paroxetine that have less inhibitory effects to prevent excessive sedation with benzodiazepines [24].

8.3. Muscle damage (rhabdomyolysis)

When the striated muscle disintegrates and the related myoglobin enters the blood and then urine it leads to renal failure [24]. Infections, ischemia, blunt force trauma usually cause it [24]. Heroin, solvent abusers and statin treatment may also cause it [24]. When cerivastatin used along with gemfibrozil led to rhabdomyolysis [24]. However cerivastatin, lovastatin,simvastatin are 3A4 substrates and increase plasma levels in presence of potent 3A4 inhibitors such as grapefruit juice, azoles and erythromycin [24]. If statins need continued in presence of 3A4 inhibitors then it would be wise to use fluvasatin and pravastatin which are readily cleared by CYPs [24].

8.4. Excessive anticoagulation

Warfarin being the most widely used anticoagulant is given in two forms the S- form being more potent than the R- isomer [24]. The clearance of drugs occur sterioselectively, with 1A2 and 2C19 metabolise R-isomer and 2C9 the potent S-isomer [24]. Cimetidine an effective inhibitor of 1A2 and 2C19 is not recommended as there is potential for moderate increase in the prothrombin time [24]. The other drugs which inhibit warfarin metabolism and lead to increase in prothrombin time are sulphamethoxazole, trimethoprim, amiodarone , statins and disulfiram thus causing GI tract bleeding and intracranial haemorrhage [24].

9. Use of inhibitors in positive clinical intervention.

The inhibitors may benefit the patient in the form of preventing the formation of toxic metabolite, reducing the hormone levels in cancer chemotherapy or even to reduce the cost of prescribing an expensive drug [24].

9.1. Use of inhibitors to arrest hormone-dependant tumours

This type being the most successful clinical application of inhibitors of CYP mediated metabolism [24]. Two treatment approaches has been found out for the breast cancers [24]. The first strategy is to block the receptors (tamoxifen) and the other to prevent the oestrogen from being formed from the androgenic precursors [24]. The oestrogenic molecule is vulnerable to aromatase mediated reactions and the first aromatase inhibitor developed was aminoglutethemide, effective but led to various hematological problems [24]. Later Ketoconazole was found to retard progression of breast cancer, but produced hepatotoxicity [24]. The latest developments are Anastrazole, exemestane and letrozole [24]. They showed serious of side effects as nausea, weight loss and

hot flushes and later third strategy of drugs to fight hormone dependant tumors by degrading and destroying oestrogen receptor [24]. The most effective of these agents is Faslodex [24].

9.2. Use of inhibitors to reduce toxic metabolite formation

They are lot of P450 mediated reactions which would lead to toxic products capable of severe toxicity due to the oxidation of metabolized molecule which becomes unstable and highly reactive [24]. The best example being, paracetamol overdose leading to quinine-imine derivatives resulting in necrosis of liver [24]. Thus glutathione supplements such as N-acetyl cysteine could prevent necrosis to some extent [24]. Later inhibitors were incorporated in paracetamol tablet as majority of clearance takes place by sulphation and glucuronidation [24]. However another route of inhibition is the use of GST inhibitors in combination with N-acetyl cysteine may rescue those previously doomed in liver failure or GSH directly to detoxify reactive metabolite N- acetyl parabenzoquinenimine (NAPBQI)[24].

9.3. Use of inhibitors in alcoholism

The potent inhibitor of aldehyde dehydrogenase and CYP2E1 known as disulfiram is used as treatment of alcoholism to help the abstinence process [24]. Alcohol is metabolized by alcohol dehydrogenase and CYP2E1 to acetaldehyde which is cleared by aldehydedehydrogenase to acetic acid and water [24]. When disulfiram is given the latter step of clearance is stopped and large amount of acetaldehyde accumulates leading to flushing, nausea and vomiting [24].

10. ENZYME INDUCTION

Enzyme induction results due to increase in the enzyme activity and may occur when the hepatic blood flow is increased or the synthesis of more CYP450 enzymes is stimulated [18]. Inducers are lipophilic in nature and induction depends upon time required for enzyme degradation and new enzyme production [18].The ability to induce drug metabolism is affected by age and patients with cirrhosis and hepatitis are less susceptible to enzyme induction [18].

10.1 Drug metabolizing enzyme induction in humans

The most common mechanism is transcriptional activation leading to increase in CYP450 enzyme proteins [15, 16, 19]. If drug induces its own metabolism, called as auto induction and if metabolism is induced by other drug called as foreign induction [15, 16, 19]. The metabolism of the induced drug is increased leading to decreased intensity and duration of drug effects [15, 16, 19]. If drug is a pro drug and is metabolized to active or toxic metabolite the level of toxicity is increased [15, 16, 19].Enzyme inducers are those drugs which increase the metabolism of other drugs and the most affected are the drugs metabolized by CYP3A4 and CYP2C9 [15, 16, 19].

Enzyme inducers may increase the formation of toxic metabolite thus leading to hepatotoxicity and toxicity to other organs [15, 16, 19].

Drug metabolizing enzyme induction in humans

	Daily dose(mg)	Day of treatment when altered drug metabolism is determined	Drug affected
Phenobarbital Therapeutic dailydose:50-200mg	120 210 90 2mg/kg 10-20µg/ml of blood	21 2 14 14 28	Warfarin Warfarin Bishydroxycoumarin Antipyrine Quinidine
Carbamazepine Therapeutic dailydose:800-1200mg	300-1200 400-600 200	60 80-90 4	Carbamazepine Antipyrine Clonazepam
Chlorpromazine Therapeutic dailydose:100-1000mg	300 300 300	14 7-14 7-14	Chlorpromazine Chlorpromazine Antipyrine
Diphenylhydantoin Therapeutic dailydose:600mg	600 600 300 300	14 5 3 22	Cortisol Digitoxin Dicoumarol Antipyrine
Phenylbutazone Therapeutic dailydose:200mg	300	3-5	Digitoxin
Rifampicin Therapeutic dailydose:600mg	600 600 600 900 600 600 600 150-600	Long term 7-14 Long term 4-5 7 6 28 9	Rifampicin Rifampicin Warfarin Acenocoumarol Antipyrine Antipyrine Tolbutamide Tolbutamide
Testosterone Therapeutic dailydose:5-15mg	400 400 400	21 21 21	Antipyrine Antipyrine Antipyrine

TABLE 3: Drug metabolizing enzyme induction in humans[23].

11. Induction- general clinical aspects

Two major aspects to be considered

1. Altered drug metabolism leading to either reduced or enhanced drug action [23].
2. Changes in the metabolism of endogenous compounds with consequent production of organic lesions [23].

11.1. Anti- epileptic agents

11.1.1. Drug combinations

In approximately one-third cases of epilepsy condition is controlled by combination of carbamazepine (2C9,2C19,3A4), Phenytoin (1A2,3A4) and phenobarbitone (1A2,2C8,3A4) [24].In combination with anticonvulsants the other co administered compounds metabolized by CYP enzymes have their plasma concentration reduced by 80% in case of valproic acid in presence of phenobarbitone and 50% in case of phenytoin and 70% with carbamazepine [24].

11.1.2. Drug withdrawal

There may be problems when the combination of anticonvulsants is changed, or either drug is completely withdrawn [24]. They will be rise in drug plasma levels as such and intensification of pharmacological effect becomes apparent. It is apparent if we can anticipate the effect by tapering the dosage over the days or weeks as appropriate [24].

11.2 Anticoagulants

Anticoagulants such as warfarin mainly depend on CYP2C9 for their clearance along with some effect from CYP 3A4 and 1A2 [24]. Inducers of this drug will increase its clearance and therefore affect their anticoagulant effects and if the inducer is withdrawn there is possibility of accumulation of anticoagulant leading to haemorrhage [24].

11.3 Anti-cancer drugs

Increase in the plasma levels of antineoplastics such as cyclophosphamide and taxol in presence of 3A4 inducers [24]. Up to threefold increase in clearance of antineoplastics has been seen in presence of 3A4 inducers [24].

11.4. Antiviral drugs

The newer anti–HIV agents are all metabolized by CYP3A4, inducers thus affect their clearance in vivo [24].Ritonavir is potent inhibitor of CYP3A4 and initiates its own metabolism [24]. Rifampicin may affect its plasma level concentration but only to modest degree [24]. Thus changes in the antiviral agents or antibiotics must be closely monitored for minimum inhibitory concentrations and toxicity is minimized [24].

11.5. Oral contraceptives

Oral contraceptive such as ethinylestradiol clearance is increased in presence of 3A4 inducers, which is important in low dose contraceptive preparations [24]. Increasing the dose may negate this effect [24]. Other corticosteroids are also cleared rapidly in presence of CYP3A4 [24].

12. CONCLUSION

Of the various potential causes interaction at the metabolic site results in the increased or reduced conversion and elimination with possible clinical consequences. Although genetically determined iatrogenic diseases and interindividual variation affect drug metabolism, the observed adverse effects result from the drug-drug interactions at metabolic sites. Clinicians should be aware of the potential interactions and become familiar with the substrates, inhibitors, and inducers of the common enzymatic pathways responsible for drug metabolism. By understanding the unique functions and characteristics of CYP enzymes, physicians will be able to anticipate and manage drug interactions. This will enhance the use of rational drug therapy and better drug combinations.

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