Journal of Drug Metabolism and Toxicology

Singh et al., J Drug Metab Toxicol 2018, 9:1
DOI: 10.4172/2157-7609.1000233

Review Article Open Access

Metabolism of Drugs with Inhibition of Enzymes

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Abstract

Drug metabolism is a process which is very important for the living organisms and thus provides various metabolic sites at various levels. The major site for the metabolism of drug is liver, whereas the first pass metabolism occurs. Enzymes usually catalyse every biochemical process inside the body. This review focuses on the metabolism of drugs with the need of inhibition of enzymes showing new developments in the art of enzyme inhibition. It shows methods for the inhibition of enzymes with the use of enzyme inhibitors as therapeutic agents and antimicrobial agents. It also shows the various effects like of ethanol, tobacco and diet on the metabolism of drug. It also describes the aapplication of competitive inhibitors in Pharmaceutical medicine with the help of COX-1 and COX-2 enzyme inhibitor. The differences in between COX-1 and COX-2 inhibitors have also been described in this review with the effect of aspirin on COX.

Keywords: Metabolism; Catalyse; Inhibition; Competitive inhibitors.

Introduction

Metabolism of drug is a biological process of drugs by the body, normally done with specific catalyst systems. The pharmaceutical metabolisms of drugs are an essential prospect of pharmacological medicine. The metabolism rate of a drug describes the time period and potency of a drug pharmacologic action. Most of the production of drug metabolism are inactive than the main compound. In some cases, may be, the responsibility is of the metabolites for deadly, mutagenic, teratogenic or cancerous effects [1]. For example, burden of acetaminophen build on their hepatotoxicity to a minor matter which then reacts with the proteins present in the liver. In few cases, with the metabolism of so-called prodrugs, substances are mainly the active remedial compounds. The best example of a prodrug is given by cyclophosphamide, an inactive conjugate which gets metabolized by the liver into an extremely passive anticancer drug [1].

Organ level

The leading organ is liver for the metabolism of drug. The gastrointestinal tract is very important extra hepatic site. The orally administered drugs are bound greatly in the intestinal epithelial tissue, that results in reduce bioavailability [1]. The lung, kidney, intestine, skin and placenta can also transfer the drug metabolized activity. Because of its tremendous percussion rate and its anatomical location with respect to the circulative system, the lungs may apply a first-pass effect for drugs administrate IV [2] (Figure 1).

Cellular level

Most of the catalysts concerned in drug metabolic process are placed within the lipotropic tissue layer of the smooth endoplasmic reticulum. When the SER is confined by tissue homogenation and centrifugation in the laboratory, the SER tissue layer re-form into sac called microsomes [1]. Since many enzymes carry out oxidation state, this SER tangled is mentioned as the microsomal mixed function oxidase (MFO) system [2] (Figure 1).

Biochemical level

Phase I reactions are those reactions which change a drug to a more polar dissected compound by introduction of a charged structural groups such as -OH, -NH_2, or -SH. The Phase I production are still not eradicated speedily and hence go through Phase II activity referring conjunction of the recently accepted polar unit with endogenous compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids. The formation of Glucuronide is considered to be most common in phase II reaction [2]. In the past, the parent drug may be considered to undergo phase II conjugation immediately. In few cases, a drug may go through a series of successive reactions that results in the making of tons of substances. Many phase I MFO biotransformation activity are aerophilic in existence and they need a reducing agent (NADPH) and a compound of microsomal catalyst; the concluding oxidizing catalyst is called cytochrome P450, a hemo protein that is named because of its carbon monoxide derived from it absorbs light at 450 nm. As the cytochrome P450 is in reality a family of catalyst which is different from the primarily with respect to their surface particularity. Advancement in molecular biology has lead to the identity of more than 70 well-defined P450 genes in respective species [3]. The terminology of the P450 enzyme products has transform complex. Based upon their amino acid similarity, the P450 reductases have been classified into families such that a cytochrome P450 from one family unit exhibits<40% amino acid succession recognition to a cytochrome P450 in some other gene family unit. Various kinds of gene families are far separated into subfamilies, lined by letters A, B and C etc. Eight main mammalian gene families have been outlined are as follows in below Table 1.

Site/Organs of drug metabolism

The major site of drug metabolism is Liver. Secondary organs are: Kidney, Lungs and Skin.

First pass metabolism

The ability of the liver and extra hepatic tissues to metabolize the substance to either into pharmacologically inactive or bioactive metabolite before reaching the systemic blood circulation is known

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Received April 02, 2018; **Accepted** April 23, 2018; **Published** April 30, 2018

Citation: Singh V, Sharma PK, Alam MDA (2018) Metabolism of Drugs with Inhibition of Enzymes. J Drug Metab Toxicol 9: 233. doi:10.4172/2157-7609.1000233

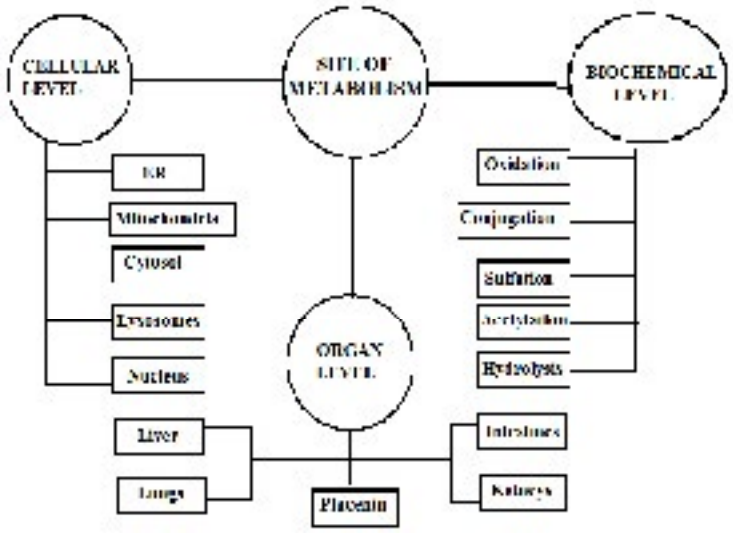

Figure 1: Sites of metabolism of drug.

P450 Gene Family/subfamily	Characteristic substrates	Characteristic inducers	Characteristic inhibitor	Reference
CYP 1A2	Acetominophen	Tobacco	Cimetidine	[4]
	Estradiol	Char-Grilled Meats	Amiodarone	
	Caffeine	Insulin	Ticlopidine	
CYP 2C19	Diazepam, Omeprazole	Prednisone	Cimetidine	[5]
	Progesterone	Rifampin	Ketoconazole	
			Omeprazole	
CYP 2C9	Tamoxifen	Rifampin	Fluvastatin	[6]
	Ibuprofen	Secobarbital	Lovastatin	
	Fluoxetine		Isoniazid	
CYP 2D6	Debrisoquine	Dexamethasone	Cimetidine	[7]
	Ondansetron	Rifampin	Fluoxetine	
	Amphetamine		Methadone	
CYP 2E1	Ethanol	Ethanol	Disulfiram	[8]
	Benzene	Isoniazid	Water Cress	
	Halothane			
CYP 3A4, 5, 7	Cyclosporin	Barbiturates	Cimetidine	[9]
	Clarithromycin	Glucocorticoids	Clarithromycin	
	Hydrocortisone	Carbamazepine	Ketoconazole	
	Vincristine	St. John's Wort	Grapefruit Juice	
	Many others		Many others	

Table 1: Major names of Cytochrome P450 Gene families [4-9].

as first pass metabolism. Most of the orally given drugs are known to undergo the liver first pass metabolism during their transit to the systemic circulation from the gastro-intestinal tract [4-10]. Thus, the liver can remove the substances from the gastrointestinal tract, thereby preventing distribution to the other parts of the body [11].

- Lesser the oral bioavailability of a given drug, it may be the results of either presystemic intestinal metabolism or hepatic first pass metabolism or conjugation reaction.
- Other routes of administration for susceptible drugs that have been look into in an attempt to overcome the noticeable pre systemic metabolism [11].

The ways that are used to bypass first pass effect refer gifting the drugs by two way i.e sublingual and buccal routes.

The various drugs are mainly absorbed orally in these methods. In the organization of sublingual, the drug is been below the tongue where it resolves the salivary release. The administration of Nitroglycerine is also been done in the same way.

In the administration in the buccal, the drug is been placed in between the teeth and mucous sheet of the cheek. In both methods they are confront for the termination by the fluids of GI and the liver's first pass effect [10,11].

Enzymes Responsible for Metabolism of Drugs

Luminal enzymes

There are two phases to the digestive process going on at the same time in the organism. The luminal phase, which takes place in the

lumen of the digestive tract and is based on the first hydrolysis of large particles into smaller particles. This phase is carried out by the acid that has been secreted in the stomach and by the various varieties of enzymes secreted either by the stomach, pancreas or intestine [11].

Mucosal enzymes

These are the most important enzymes for the small intestine as they are the most active tissue in the body. The mucosa of the small intestine contains clear-cut morphological functions. The mucosal cells are highly distinguished for the digestion and absorption [11].

Bacterial enzymes

These enzymes are proteins that are bacterial whose functions mainly consider catalytic transactions. These enzymes are produced by bacteria that have many specific and toxic effects [11,12].

Effect of ethanol on drug metabolism

The administration of ethanol is very important as it can both inhibit and enhance the metabolism of drug. It is metabolised normally by the alcohol in the cytosol and dehydrogenase. It is also metabolised by an inducible microsomal enzyme. The microsomal oxidising system of ethanol was induced by chronic administration of ethanol [13]. The drug metabolising enzymes and the alcoholics usually metabolise the drugs like tolbutamide, warfarin and phenytoin more frequently than the other non-alcoholics [14]. On the other side, acute administration of ethanol to the volunteers decreases the clearance of warfarin [15].

The effect of tobacco smoking on drug metabolism

The effect of smoking on metabolism of drug is inductive and it is found that the concentration of plasma of phenacetin were less in smokers as compared to non-smokers [16]. It has been suggested that on metabolism of drug the effect of smoking cigarette mainly occurs in the young as compared to the elders [17]. Although it is considered as an elective process i.e. effect of smoking. At the present time it is not possible for the prediction which drug will be affected. The habit of smoking is considered as one of the primary sources for the interactions of drug in human being. Over more than 3000 chemicals are so far been identified in the smoking of cigarette, the hydrocarbons that are polynuclear aromatic are the responsible agents for the induction of enzyme which is hepatic [18].

The effect of diet on drug metabolism

Many investigations have been made and are shown that the diet play an important role in the determination of the metabolising capacity of the drug for the individual. It has been shown that the ingestion which is continued for either charcoaled broiled beef or brussel sprouts significantly increased the metabolism rate of various drugs [19]. The identification of the specific inducing agent was not done.

Need of enzyme inhibition

Enzyme is known molecule of protein that display activity of specific and affinity of binding with the molecule of substrate that completes reaction of enzyme or bio chemical process. Similarity of substrate may suppress the reaction of enzyme and their enactment is like inhibitor of enzyme. Inhibition of enzyme means loss of an action of enzyme on location that is specific for enzyme site that is progressive by substrate that is specific, they are called enzyme inhibitor [20]. In present, many health professional as well as nutraceutical are socio-economic class as inhibitors of enzyme and these exhibit their particular state in the inhibition of enzyme inside the various cells and body of human being. The enzyme inhibitors actions in the discovery of drug has turned a novel coming at any pharmaceutical industry in the field of pharmacology, research lab of university or research center of drug. The issue that is latest is been compiled from the data of various sources with the purpose of merging a large extent of idea of basic and practical inhibition of enzyme assessment performing in the drug discovery [21]. The enzyme inhibitors are well-advised to be chemical compounds whose molecular weight is low. They also trim down the catalytic activity of the enzyme which is either reversible or irreversible. Inhibitors can alter one amino acid, or many side chain (s) which is needed in catalytic enzyme activity. The protection of catalytic site of enzyme by doing any alteration, binding of ligands with the side chain of hypercritical present in the enzyme. The alteration of chemical is to be done for testing the inhibitors for any value of drug. In discovery of drug, many drugs are chosen parallelly and are planned for the inhibition of enzymes that are specific [22].

New evolution in the creation of inhibition of enzymes

In this present time, enzymes that are immobilised are utilized in commercial enterprise and they are worth as medicative and industrialized products of enzyme. The appearances of the newly made activator in the discovery of drug, many new executions are awaited in proceeding of fresh analogues of substrate. The new enzyme substrate progressive sites with fundamental interaction are owed to various intricacies of binding [22].

Slow-tight inhibition: This type of suppression happens when the basic complex of enzyme-inhibitor EI go through changes that are conformational with the much more constricting complex that are binded. The whole process of inhibition is volatile. It was supposed to be themselves as easy accelerating inhibition of enzyme. Below the situations, conventional Michaelis-Menten mechanics provide a wrong duration of a time-dependent K_i. The real amount of K_i can be acquired finished with more tangled reasoning of the on (k_{on}) and off (ko_{ff}) constants of rate for the association of inhibitor [23].

Substrate and product inhibition: This biological process is done when the matter or outcome of a reaction of enzyme suppress the activity of enzyme. The suppression travels to the competitory, noncompetitive or miscellaneous forms. In this suppression there was a gradual decrement in act of leading concentration of substrates [23].

The indication of the state of given below the binding of substrate places present in the enzyme. In the degraded substrate, the advanced-attraction tract is engaged and average mechanics was preceded. Yet, at high density, the inhibition site that is second becomed engaged, with inhibition of enzyme. Inhibition of product was frequently a regulative property in biological process and can be in a shape of neutral response [24].

Antimetabolites: The chemical substances that interact with the biological process that is normal of regular metabolites that are biochemicals. They are present in mostly all happenings and that is because of the functional sameness to the substrates that are physiological and hence known as competitive inhibitors of enzymes. The consist of antifolates and examples are hydroxyl urea and pyrimidine and purine analog. The main use of it is for cytotoxic anticancerous drugs through with suppressing DNA and RNA chemical process and division of cells [25].

Antienzyme: The parasites that are present in the intestine, example: Ascaris, assist itself from biological process by expliciting on the surface of matters which are in nature to be considered as proteinacious substance that supress the act of enzymes that are digestive. The blood in plasma and the fluids present in extracellular

are including many kinds of inhibitors that are protease are very much essential for dominating the formation of blood clot, dissolving, enclosure and homeostasis of cytokine. Mostly the inhibitors may be peptides and many of these are separated from various sources of plants [25]. Mostly natural peptides of inhibitors of protease are connected in construction with the sequence of amino acid of the substrates of peptide of the enzyme. The peptide protease inhibitors that are designed are very essential drugs. Inhibition of the enzyme is kept activated for angiotensin and hence precludes the vasoconstriction for making the blood pressure low [26].

Antibodies: They are against many non-usable enzymes of plasma that contain clinical characteristic that are important since they have long life as compared to itself with enzyme and therefore they indicate the history of disease finer. The autoimmuned antibodies are considered to be medically essential in identification of the autoimmuned sickness [27].

Biosensors: Inhibition of light almost in every activity of enzyme was although because of few catalyst. The denaturation of many enzymes are because of ultraviolet rays and ionization radiations. Almost many catalyst carry groups that are sulfahydryl (-SH) at the sites that are active which when oxidizes by the help of oxidants and the radicals which are free by oxidants and the radicals which are free demobilizes the enzymes [28].

Methods of Inhibition of Enzymes

There are mainly three methods of inhibition – Competitive, Uncompetitive and Non-competitive.

Every type of inhibition forms a different type of rate of equation.

Reversible enzyme inhibition

The inhibitor that is reversible mainly separate very quickly from the enzyme through which it has been targeted because it transforms really loosely conjugated with enzyme. The various kinds of inhibition that are reversible are dignified: competitive, noncompetitive and uncompetitive [29].

A. Competitive or substrate analogue inhibition: It mainly happens at the site that is active. The enzyme (E) usually combines, by formation of an enzyme-inhibitor (EI) complex instead of an ES complex. The substance contends with the substratum to combine with the catalyst. The grade of biological process mainly look upon the relational density of the substance and the matter [28,29].

This has been noticed that in this, the binding of substrate with enzyme (forming an ES complex) or inhibitor (EI), but not both one (ESI). We noticed that an inhibitor that is competitive decreases the rate of the reaction by losing the proportionality of the molecules of the enzyme that are in bonds with the substrate. This can be examined by steady-going mechanics quantitatively. As the matter binds reversibly with the enzyme, the contest can be partial to vantage the substratum solely just by addition of many substratum. When the substrates are present in more amounts, the chance of the molecule of inhibitor that it will be binding is decreased and the response displays a regular V_{max}. Hence, the [s] at which V_0=1/2 V_{max}, the K_m will gain in the existence of inhibitor [29].

B. Noncompetitive inhibition: No challenge happens between the substrate, S and the inhibitor; I. The inhibitor has likeness that is small or have no structure with the substrate and it bounds with enzyme at a point other than the site that is active and known as the allosteric site. Since I and S may combine at various opposite sites, making of both EI and ESI complexes takings place. Both ES and ESI broke downward for the production of the reaction product (P). It is noted that in this, both inhibitor and substrate can bind at the same time to the molecule of an enzyme since the binding sites are different and they do not converged. The enzyme is not activated when substance is bound, whether or not substance also exists. It is apparent that a non-competitive inhibitor acts by reducing the turnover rate rather than by decreasing the dimension of molecules of enzyme that are in bonds with the substratum. Non-competitive inhibition, in comparison with competitive inhibition, cannot get over by acceleratory concentration of substrate [30].

C. Uncompetitive inhibition: This substance also bounds at an allosteric site but the binding take point merely with the enzyme-substrate (ES) complex and not the independent molecule of enzyme.

Irreversible enzyme inhibition

This inhibition was formerly place in a class and tried as non-competitive suppression, it has been declared as a clear-cut variety of inhibition. These inhibitors are those that merge with or destruct a useful unit of the catalyst that is necessary for its act. This type of inhibitor divided into really easy from its enzyme that is targeted because it transforms really closely conjugated to its site that is active, hence inactivates the molecule of enzyme. The attachment between the inhibitor and enzyme considered to be covalent or non-covalent [29,30].

Mechanism of competitive inhibitors action

Competitive inhibitors are the compounds that match to the substrate structurally and claim with substratum for the site that is active for the enzyme to shape an enzyme-inhibitor complex. Once the substance fills the site that is active of the enzyme it cracks constricting of the substratum and dissolves the making of metabolic product that is normal. Inhibitor checks reversibly the enzyme and because of the contest that can be reduced by addition of many substrate.

The Michaelis-Menten constant in the presence of competitive inhibiton, K_m will increase [30] (Figure 2).

Enzyme inhibitors as therapeutic agents

Many therapies of drug are based on the inhibition of the action of hyperactive enzymes. If an enzyme that is overactive can be inhibited, the procession of illness can be worn-out and evidence can be alleviated. The service of substance as agents of pharmaceutical is founded on the movement of competitive enzyme inhibition [31].

In improving to compounds that are active as pharmaceutical agents, prodrugs are desirable. Prodrugs are not efficacious till they metabolise and regenerated to a form that is active. Few inhibitors can interact by the *in vivo* transformation of prodrugs if given at the same time, loss of the effectivity of the last mentioned For example, tamoxifen, the anticancer prodrug, needs cytochrome P450 2D6 to transform to an active drug [32].

Enzyme inhibitors as antimicrobial agents

Interactions of the drug with antimicrobials mostly occur during the acute infection treatment which a patient receives through other drugs. The adverse effect can be usually avoided, if the interaction is anticipated. For the interactions of the antimicrobial activity that results in its reduction. The variables that are additional will determine the significance that is clinical usually includes *in vitro* susceptibility of the organism i.e. being treated, its status and

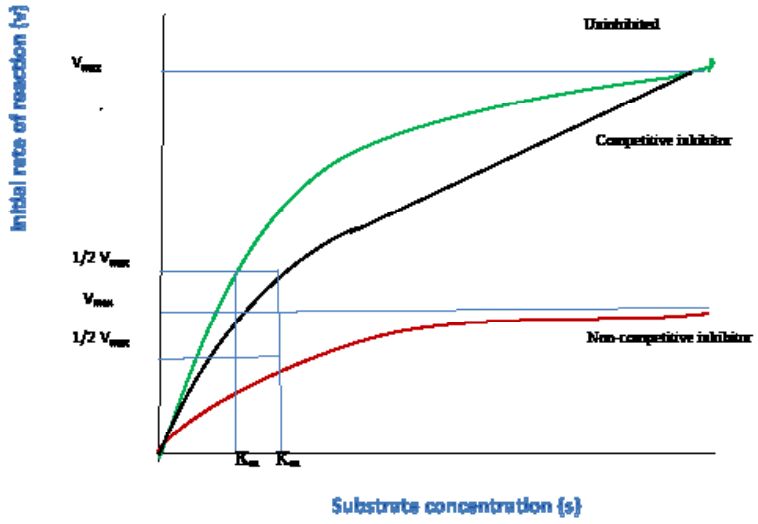

Figure 2: Initial rate of reaction (v) vs. Substrate concentration (s).

COX-1	COX-2	Reference
•They are endlessly stirred up by the body.	•Induced (normally not in present in cells).	[35]
•They are constitutional as their distribution in the body is always in stabilized form.	• They are assembled only in cells that are special.	[36]
•Creates prostaglandins used for basic housekeeping throughout body.	•Used for signaling pain and inflammation.	[37]

Table 2: COX-1 and COX-2.

location for the host defences. The antimicrobial agent may be still administered by the clinician, besides the possibilities for the occurrence of the known interaction. For some kind of interactions, especially those results in the absorption for the alteration of the antimicrobial, it is possible for the administration to move and to avoid the consequences that are not needed for the discontinuation of the other drugs temporarily [33].

Application of Competitive Inhibitors in Medicine

Enzymes that change state almost in every process in the cell and it is not unexpected that enzyme inhibitors are in the most essential pharmaceutical agents known [34].

Cyclooxygenase

It is responsible for the creation of prostaglandins. The two types, COX-1 and COX-2 includes two separate active sites are present for prostaglandin synthase. One side includes the cyclooxygenase active site. The other side contains the peroxidase active site which is concerned with the activation of the heme group essential for cyclooxygenase reaction. The compound is combined of indistinguishable dimers. Each subunit has a carbon rich node concerned in hooking the compound to the ER. The grip holds stack to sites that are trustworthy for leading arachdonic acid from the ER to the enzyme [34-37] (Table 2).

Prostaglandins

They are made from ordinary precursor particle of cyclooxygenase. The local messages are carried by significant hormones. They are made by cells that are local rather than the differentiated secretory organs like most of the secretions. They act in general areas of living cells. The controlling processes include tightness of muscle tissue and blood vessels, accumulation of blood platelet and contraction of the uterus [38].

Anti-inflammatory drugs

Many NSAIDs presently use that displays not any property to COX-1 and COX-2. This type of non selection leads to different type of side effects. Aspirin and others lead to overweening creation of the acid present in stomach as well as it leads to ulcer and bleeding in gastrointestinal [39]. The recent investigation has been oriented at the selection of COX-2 in place of COX-1 [40].

Effect of aspirin on COX

Aspirin irreversibly affects the binding site of the COX by foreclosing the manufacturing of prostaglandins [40]. The constriction of COX-1 suppresses the production of prostaglandin that is accountable for the assistance of formation of platelet that causes the bloodline to capillary and low clottation. Constriction of COX-2 let down unhealthy consequences [41]. In one research paper, COX-2 inhibition for aspirin induced asthma was studied using Nimesulide as an obstacle. The study of Meloxicam, Celecoxib and Rofecoxib has also been done in this paper [42]. The inhibition of COX-3, a cyclo oxygenase-1 variant by acetaminophen was studied for DIA (drug inhibition assays) in which infected cells were cultured for 48 h but pre incubation with drug for 30 min at 25°C was performed and final supernatant was assayed for COX activity by RIA (radio immune assay) and final inhibition curves were plotted and IC_{50} values were determined [43].

Conclusion

This review represents various metabolisms of drugs showing its activities with the effect of various enzymes. It also describes cytochrome P450 families with influence of the first pass metabolism of drugs. It shows its activities at various levels with the sites for the metabolism of drugs. The enzymes that are responsible for the metabolism with its need for the inhibition are also included. It also shows the effect of enzyme as various agents such as therapeutic agents and antimicrobial

agents. The effect of COX-1 and COX-2 is also been given for showing the application of competitive inhibitors in medicine. Lastly, it also shows the effect of COX on aspirin by describing its application.

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