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Review Article

Consequences of Drug Interactions: A Concised Review

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ABSTRACT

Drug-drug interactions arise when the effects of one drug are altered by the co-administration of another interactions are classified as pharmacokinetics -related ,where drug absorption, distribution, metabolism or excretion is affected, or pharmacodynamics-related ,when drugs with similar pharmacological actions are co-prescribed .In pharmacodynamic interactions synergism effect causes increased drug efficacy it causes toxic effects to the body, antagonism effect causes therapeutic failure of the drug. These can be complex and time dependent nature. A found knowledge on drug interaction and their mechanism is required for optimal therapy. In drug interactions enzymes also play a key role in drug interactions. Either by induction and inhibiting mechanisms. Mechanisms involved in enzyme induction may be increased enzyme synthesis, decreased rate of enzyme degradation, enzyme stabilisation or enzyme Inactivation. Mechanism involved in Inhibition decreased drug metabolising ability of an enzyme .The present review mainly focuses on the way in which the pharmacokinetics and pharmacodynamics gets altered in various conditions and mechanisms involved in drug interaction.

Keywords: Drug-Drug interactions, Enzyme induction, Enzyme inhibition, Pharmacodynamics, Pharmacokinetics.

1. INTRODUCTION

Drug interactions are said to occur when the pharmacological activity of drug is altered by the concomitant use of another drug or by the presence of food, drink or environmental chemicals [1]. the drug whose activity is affected by such an interaction is called object drug .the agent which precipitates such an interaction is referred to as the precipitant drug interactions are generally quantitative where by the intensity of effect is changed can increase or decrease and seldom quantitative. An enhanced

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pharmacologic activity can be seen in Haemorrhagic tendency of warfarin when phenylbutazone is given subsequently. Decreased therapeutic activity is observed with loss of efficacy resulted due to decrease in therapeutic activity of tetracycline when concomitantly administered with food, antacids or mineral supplements containing heavy metal ions.

2. MECHANISMS OF DRUG INTERACTIONS

The three major mechanisms cancauses an interactions develop are:

1. Pharmacokinetic interactions.
2. Pharmacodynamic interactions.
3. Pharmaceutical interactions.

Pharmacodynamic Interactions:

Pharmacodynamic interactions are those in which the activity of the object drug at its site of action is altered by the precipitant. These interactions may be direct & indirect.

Direct Pharmacodynamics Interactions:

It is one in which drugs having similar or opposing pharmacologic effects are used concurrently. The following are the three consequences of direct interactions.

Antagonism:

The condition of the interacting drugs having opposing actions is called Antagonism. This can be seen Acetylcholine with Noradrenaline have opposite effects on Heart rate .another example is Antiparkinson drug Levodopa action can be antagonised by dopamine antagonist, haloperidol & cholorpropamide.

Additive effect (or) Summation:

The condition in which the interacting drugs have similar actions and resultant effect is the sum of individual drug responses is called Additive effect. This is happens Hydrocortisone with Hydrochlorthiazide together can produce additive side effects of hyperglycaemia or hypokalaemia. Another example co administration of salicylates &anticoagulants result in the increased risk of bleeding.

Synergism:

The condition of enhancement of action of one drug by another drug. This can be seen Alcohol enhances the analgesic effect of aspirin. Another example oestrogen with Warfarin leads to increased anticoagulation.

Indirect Pharmacodynamic Inetractions:

Indirect Pharmacodynamic in both the object and the precipitant drugs have unrelated effects but the precipitant. Drug in some way alters the effects of the object drug.this effect can seen in salicylates decrease the ability of platelets to aggregate thus impairing the haemostasis of warfarin induced bleeding occurs. The resultant effect of all pharmacodynamic interactions is thus altered with drug action change in plasma concentration.

Pharmaceutical Interactions:

It is a physicochemical interaction that occurs. When drugs are mixed in intravenous infusion causing precipitation or inactivation of the active principle such interaction are expressed by the term compatibility.

Ex : Ampicillin with dextran in solutions and are broken down (or) form chemical complexes .

Pharmacokinetic Interactions:

[8]These are those in which the absorption; distribution; metabolism and or excretion (i.e..,ADME) of the object drug are altered by the precipitant. The resultant effect is altered plasma concentration of the object drug. These are most common and often result in differences in pharmacologic effects. Clinically; important effects are precipitated by drug having low therapeutic indices (digoxin).

Interactions affecting absorption of drugs:

[2] Drug distributions can affect drug absorption by effecting the dissolution of the drug in the stomach by influencing gastric emptying or intestinal blood flow or by inhibition of active transport processes. Certain drug combinations can affect the rate or extent of absorption of anti-infective by interfering with one or more of these mechanisms [3] .generally a change in the extent of a medication's absorption of greater than 20% may be considered clinically significant [4] drug dissolution in the stomach can be modulated by gastric ph. changes or by complexation or chelation of drug.

[3] **Change In P^H:**

The degree of absorption ionisable drug from the stomach or duodenum depends on the pka of the drug and the P^H of the environment. In general alkalization agents such as bicarbonate salts decreases the absorption of weak acids (NSAIDS, Vitamin antagonists); having a pka between approximately 2.5 and 7.5.

Acidifying agents such as citric and tartaric acids affects the absorption of weak bases having a pka between approximately 5 & 11 (propoxyphene & reserpine) .

Effects of Gastric Emptying:-

Gastric empting controls the length of time that a drug remains in the stomach. The longer a drug remains in the stomach; the slower it is absorbed increasing the rate of gastric emptying increases the rate of drug absorption.

Effects of Intestinal Blood Flow:-

Intestinal blood flow can be the rate limiting step in the absorption of some lipophilic drug

Ex: intestinal blood flow can be modulated by vasodilation and vasoconstrictors and hypothetically affect the absorption of lipophilic drugs.

Complexation and Chelation:

Some drugs can interact to form complexes that are poorly absorbed.all these exmples of drug interactions affecting absorption tabulated below.

Table 1: Influence of drug interactions on Absorption of Drugs

Condition affecting absorption of	Object drug	Precipitant drug	Influence on Object drug

drugs			
Change in Ph.	Sulphonamides Aspirin	Antacids	Enhance dissolution & absorption rate
	Ferrous sulphate	Sodium bicarbonate ,calcium carbonate	Decreased dissolution & enhance absorption
	Ketoconazole ,tetracycline Atenolol	Antacids	Decreased dissolution &bioavailability
Complexation &chelation	Ciprofloxacin Norfloxacin	[12]Antacids containing al,mg,ca,sucralfate	Reduced absorbance due to complexation with metal ions.
Adsorption &complexation :	Cephalexin Sulphamethoxazole :Trimethoprim Warfarin Thyroxin	Cholestyramine	Reduced absorption due to absorption & binding.
Effect of gastric emptying	Aspirin Diazepam,levodopa Lithium carbonate Paracetamol Mexeletine	Metoclopramide	Rapid gastric emptying increased rate of absorption.
	Levodopa Lithium carbonate,mexilitine	Anticholinergics Atropine	Delayed gastric emptying decreased rate of absorption.
Alteration of G.I.microflora	Digoxin	Antibiotics Erythromycin Tetracycline	Increased bioavailability due to destruction of bacterial flora that inactivates digoxin in lower intestine.
	Oral contraceptives	Antibiotics Ampicillin	Increased reabsorption of drugs secreted as conjugates via bile in the intestine.
Malabsorption syndrome	Vitamin A,B12,Digoxin	Neomycin Colchicine	Inhibition of absorption due to malabsorption caused by neomycin.

Interactions affecting distribution of drugs:

Drug distribution also gets affected by the drug interactions which results due to competition between drugs for binding to proteins, tissues and displacement of the drug by another drug [8]. Competitive Displacement which results when two drugs are capable of binding to the same site on the protein causes the most significant interactions. Greater risk of interactions exist when the displace drug is highly protein bound (>95%) has a small volume of distribution and has narrow therapeutic index (warfarin) and when the displacer drug has a higher degree of affinity than the drug to be displaced. In such situations; displacement of even a small % of drug results in a tremendous increase in the free form of the drug which precipitates increased. Therapeutic of toxic effects.

Table 2: Influence of drug interactions on Distribution of drugs

Object drug	Precipitant drug	Influence on Object drug
Anticoagulants	salicylates	Increased clotting time and increased risk of haemorrhage by the displacement of warfarin from its protein binding site.
Methotrexate	salcylicacid	Increased methotrexate toxicity.
Phenytoin	valproicacid	Phenytoin toxicity.
Sulfonylurea's (tolbutamide)	Insulin	Exerts therapeutic effects by displacing insulin from protein binding sites in pancreas; plasma and other regions resulting in its elevated levels.

3. INTERACTIONS AFFECTING DURING METABOLISM OF DRUGS

Drug-drug interactions involving metabolism are one of the principle problems in clinical practise to evaluate the pharmacological adverse effects of drugs. The most important and most common cause of pharmacokinetic interactions is alteration in the rate of bio-transformation of drugs. Major problems arise when one drug either induces or inhibits the metabolism of another drug. The enzymes mainly involved in interactions due to metabolism or the human liver microsomal P450 [6, 7] enzymes.

Induction:

The phenomenon of increased drug metabolising ability of the enzymes by several drugs and chemicals is called as enzyme induction. The agents which bring about such an effects are known as inducers. Most inducers are in general lipophilic compounds with long elimination half-life. Mechanisms involved in enzyme induction may be increased enzyme synthesis, decreased rate of enzyme degradation, enzyme stabilisation or enzyme Inactivation.

Enzyme induction generally results two major consequences: Increased metabolic clearance which results in reduced pharmacological activity or therapeutic efficacy. Activation of inactive or prodrug into an active metabolic which results in increase in concentration of active metabolite that leads to increased toxicity.

Table 3: Interaction involving enzymatic induction

CYP1A2	Caffeine, Clozapine, R-warfarin , Tacrine, theophylline
CYP2C9/10	Phenytoin, S-warfarin, tolbutamide
CYP2C19	Amitriptyline, clomipramine, Diazepam, Imipramine, Omeprazole, Phenytoin, Propranolol
CYP2E1	Chlorzoxazone, halothane, methoxyflurane
CYP2D6	Amiodarone, Amitriptyline, clomipramine, Codeine, desipramine, dextromethorphan , encainide/flecainide, fluvoxamine, imipramine, metoprolol, mexilitine, nortriptyline ,Perphenazine, propafenone, propranolol, thioridazine, Timolol

Table 4: Inducers of CYP Enzymes

All	Phenobarbital, phenytoin
CYP2E1	Isoniazid
CYP3A1	Spironolactone
CYP3A4	Carbamazepine, rifampin

2) Inhibition:

A decreased in the drug metabolising ability of an enzyme is called as enzyme inhibition. The process of inhibition is of three types.

1. Competitive
2. Non-competitive
3. Un-competitive

Inhibition Mechanism of Drug Metabolism P450:-

[9, 10] Drug metabolism by P450 can be inhibited by three mechanisms.

The first is mutual competitive inhibition caused by co-administration of drug metabolised by the same P450 isozyme.

Table 5: Interaction involving enzymatic inhibition[7]

CYP1A2	Cimetidine, ciprofloxacin, enoxacin, Erythromycin, Fluvoxamine, grapefruit juice,
CYP2C9/10	Fluconazole
CYP2C19	Fluoxetine, fluvoxamine, omeprazole
CYP2D6	Cimetidine, Fluoxetine, haloperidol, Paroxetine, quinidine, ritonavir
CYP3A3/4	Cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, miconazole, Ritonavir

1) Competition Inhibition:

It is a pattern of the inhibition where the inhibitor competes with the drug for same binding site within an enzyme protein. This competitive inhibition can be overcome by raising sufficiently increasing the concentration of substrate.

[4] It is most common type of inhibition.

E+S $\Leftrightarrow$ ES$\longrightarrow$ E+P

E $\longrightarrow$ Enzyme

S $\longrightarrow$ Substrate

P $\longrightarrow$ Product.

E+I $\Leftrightarrow$ EI

EI$\longrightarrow$ Enzyme inhibition complex.

Ki [Inhibition constant for I]

Km [Michaelis constant for S]

In the case of competitive inhibition; the metabolic rate (v) can be expressed by the following equation.

$$V = \frac{Vmax\,[S]}{[S] + Km\left(1 + \frac{[I]}{KI}\right)}$$

$$V = \frac{Vmax\,[S]}{[S] + Km}$$

Vmax = maximum metabolic rate.

I = Inhibiting agent concentration.

S = Substrate concentration.

In theophylline develop nausea and when enoxacin is added to theophylline.

The nausea is associated with an elevated concentration of theophylline caused by inhibiting the metabolism of theophylline.

The increased theophylline concentration in plasma return to pre-enoxacin value when enoxacin is withdrawn.

A more quantitative of the events may be gained from two equations.

One pharmacokinetic defines the average concentration of drug at plateau.

$$Css: avg = \frac{f \times dose}{cl \times z}$$

$$t.e = \frac{f \times x_0}{v_d \times k \times z}$$

The other equation defines the new (&longer) half-life of theophylline ($t_{1/2}$inhibition)in relation to the normal half-life ($t_{1/2}$ normal)

$$\frac{t_{\frac{1}{2}}normal}{t_{1/2}inhibited} = \frac{cl_{inhibited}}{cl_{normal}}$$

$$t_{1/2}inhibited = t_{1/2}normal = \frac{cl_{normal}}{cl_{inhibited}}$$

Where cl_{normal} and $cl_{inhibited}$ are the clearances of theophylline in the absence and presence of inhibitor; respectively Enoxacin does not affect the volume of distribution of theophylline.

The half-life of theophylline in absence of enoxacin is 8.8hrs &as expected with such a short half-life the plateau concentration($C_{avg.ss}$) is approximately 4mg/L is reached within 2days of starting the theophylline regimen.

when enoxacin added to the theophylline regimen the plasma concentration rises to a new plateau; approximately 9mg/L. determined by the new; and lower; clearance value ($Cl_{inhibition}$)according to .

$$avg = \frac{fx_0}{v_d \times k \times \tau}$$

$$\frac{c_{ss}normal}{c_{ss}inhibited} = \frac{cl_{inhibited}}{cl_{normal}}$$

$$cl_{inhibited} - \frac{c_{ss}normal}{c_{ss}inhibited} \times cl_{normal}$$

Graded effect:

The graded nature of inhibition of metabolism that for each metabolic pathway operating according to michaelis-menton constant type kinetics.

Rate of metabolite formation = Vm/Km x c.

C is the concentration of the unbound drug at the enzymes site. In terms of intrinsic clearance associated with metabolite formation;cl_{int}; f

cl_{int};f .c = f_m .cl_{int} . c

Where; fm is the fraction of the drug that is converted to a metabolite.

Rate of metabolism = $\frac{clintf \times c}{ifci/ki}$

= $\frac{fm \times clint \times c}{1 + ci/ki}$

Where C_I is the unbound concentration of the inhibitor K_I is the inhibition constant.

Lower the k_I; the more potent is the inhibitor.

The longer the half-life of an inhibitor; the more persistent is inhibition of withdrawing it.

The inhibition of theophylline by enoxacin is not an all- or -none effect; but rather; with all interactions a graded one.

The degree of inhibition varies with the plasma concentration.

Two conclusion can be drawn from the rate of metabolism;

1) The degree of inhibition of a particular pathway depends on the unbound inhibitor concentration relative to its k_I.

2) The impact of inhibition of drug elimination depends on fm and whether response lies with drug or metabolite formed.

cl inhibited = cl normal [fm /1+CI/KI + (1-fm)]

ex:-Antidepressant desipramine; metabolised by the cyp206 to form 2- hydroxydesipramine quinidine a potent inhibitor of cypd 26 blocks this enzyme; converts extensive metabolizers of desipramine to poor metabolizers.

It is important to estimate; the potential increase in exposure associated with a drug interaction; for drugs with a narrow therapeutic index. It is obtained by

$$\frac{AUC_{inhibited}}{AUC_{normal}} = \frac{f_{inhibited}}{f_{normal}}\left[\frac{1}{\frac{fm}{1+\frac{ci}{ki}}+(1-fm)}\right]$$

By rearranging; the dosing rate is given by

$$\frac{\left(\frac{dose}{\tau}\right)inhibited}{\left(\frac{dose}{\tau}\right)normal} = \frac{f_{normal}}{f_{inhibited}}\left[\frac{fm}{1+\frac{ci}{ki}}+(1-fm)\right]$$

2) Non-Competitive Inhibition:-

Non-competitive inhibition is a pattern of inhibition where the inhibitor binds to the same enzyme as the drug but the binding site is different; resulting in a confirmation changes etc of the protein.

$$E + S \leftrightarrows ES \rightarrow E + P$$

$$E + I \leftrightarrows EI$$

$$ES + S \leftrightarrows EIS$$

$$ES + I \leftrightarrows EIS$$

EIS ---->enzyme inhibitor substrate complex

It cannot be overcome by raising the substrate concentration. It is characterised by a decrease in v_m but no change in km of the substrate. It is one common type of non-competitive inhibition is mechanism based inhibited involving the formation of reactive metabolite that effectively covalently binds and permanently inactivates the enzyme. It is assumed that the inhibitor binds to free enzyme and the ES complex with the same affinity.

In this case the metabolic rate can be expressed by the

$$V = \frac{\left[\frac{v_{max}}{1+\frac{I}{ki}}\right]\times s}{km+s}$$

The degree of inhibition does not depend on the substrate concentration.

Clearance of the substrate in presence and absence of the inhibitor.

cl_f; inhibited = cl_f; normal[1/1+k_{inact} $cu_1/k_1,k_E$]

If f_m is the fraction of drug normally eliminated by the affected pathway; then.

$$cl_{inh} = cl_N\left[\frac{fm}{1+kintact\frac{cu}{k1\times k2}}+(1-fm)\right]$$

Kintact = Rate constant that relates the maximum rate of inactivation of the enzyme by the inhibitor to the amount of active enzyme remaining.

k_E = Endogenous degradation rate constant.

Uncompetitive Inhibition:-

It is a pattern of inhibiton where the inhibitor where the inhibitor binds only to the enzyme forming a complex with the drug.

$$E + S \leftrightarrows ES \rightarrow E + P$$

$$ES + I \leftrightarrows EIS$$

Unlike competitive and non-competitive inhibition the inhibitor cannot binds to the free enzyme.

The metabolic rate can be expressed by the following equation.

$$V = \left[\frac{V_{max}/(1-\frac{i}{k}1)]\times s}{\left[\frac{km}{1}+\frac{i}{k1}\right)+s}\right.$$

The inhibition becomes more market with increasing substrate concentration.

The degree of inhibition depends on the inhibition pattern when substrate concentration is high.

But when the substrate concentration is much lower than k_m (k_m>>s) the degree of inhibition (R) is expressed by following equation.

$$R = \frac{V(+INHIITOR)}{V(-INHIITOR)} = \frac{1}{1+\frac{I}{KI}}$$

In clinical situations the substrate concentration is usually much lower than k_m.

Table 6: Examples For Enzyme Inhibition

Drugs	Mechanism
Folic acid with Phenytoin	Increased absorption of folic acid due to inhibition of an enzyme responsible for its efficient absorption.
Coumarins with Metronidazole	Increased anticoagulant activity.
Oral hypoglycaemic withHypoglycaemia be precipitated. Phenylbutazone	

Non-Competetive inhibition:

Clearance of the substrate in presence and absence of the inhibitor.

cl_f; inhibited = cl_f; normal[1/1+k_{inact} $cu_1/k_1,k_E$]

If f_m is the fraction of drug normally eliminated by the affected pathway; then.

$$cl_{inh} = cl_N\left[\frac{fm}{1+kintact\frac{cu}{k1\times k2}}+(1-fm)\right]$$

Kintact = Rate constant that relates the maximum rate of inactivation of the enzyme by the inhibitor to the amount of active enzyme remaining.

k_E = Endogenous degradation rate constant.

Interactions with alcohol:

The effects of interactions between alcohol and different drugs depend on whether the consumption of alcohol is chronic (or) acute.

Table 7: Effect Of Alcohol Consumption On Various Drugs

WITH CHRONIC ALCOHOL ABUSE: The effect of anticoagulants may be dramatically decreased because of the increased rate of their biotransformation due to behaviour of alcohol as an enzyme inducer.	BARBITURATES:	Decreased sedative effect of barbiturates due to increased barbiturate metabolism.
WITH ACUTE ALCOHOL INGESTION:	ANTI COAGULANTS:	Increased anticoagulant effects of both oral anti coagulants and heparin have been reported because of decreased metabolism due to the behaviour of alcohol as an enzyme inhibitor.
WITH ANTIPSYCHOTICS +ANTI DEPRESSANTS: When combined with psychiatric drugs; clinically significant toxicological interactions may result and leading to fatal poisoning due to decreasing biotransformation.	BENZODIAZEPIES:	Decreased CNS depressant in case of concurrent consumption with benzodiazepines
	CYCLOSPORIN:	Increasing the toxicity of cyclosporin occurs.
	FELODIPINE:	Calving ADR'S. Ex: Orthostatic Hypotension.
	ISONIAZID:	Increased incidence of hepatitis.
	METHOTREXATE:	Cause hepatotoxicity.
	ASPIRIN:	Cause bleeding.
	PHENOTHIAZINES + PHENYLBUTAZONE:	Caused impaired motor coordination.

Influence of Tobacco Smoke:

Tobacco smoke is considered a self-inflicted effectors of drug metabolism. Inhalation of tobacco smoke with its more than 3000 chemical components may be considered a different way of ingesting pyrolisis products. It affects drug therapy by both pharmacokinetic and pharmacodynamic mechanisms.

Pharmacokinetic drug interactions involving the following drugs:

Pharmacokinetic interactions may call for larger doses of certain drugs due to Increase in plasma clearance, Decrease in absorption, An induction of main drug &Metabolising enzyme systems.

Examples of pharmacokinetic drug interactions:

Theophylline, Tacrine, Insulin, Imipramine, Haloperidol, Pentazocine, Flecainide, Estradiol, Propranolol,Diazepam, Chlordiazepoxide.

Pharmacodynamic drug interactions involving the following drugs:

Pharmacodynamic interactions may increase the risk of adverse events in smokers with certain pathologies such as cardiovascular (or) PUD.

However; the most common effect of tobacco smoke is assumed to be an increase in drug biotransformation through induction of specific enzyme activities.

Measurements of plasma levels of certain drugs due to increased metabolism either by the intestinal mucosa (or) first-pass through the liver.

Examples of pharmacodynamics drug interactions :

Anti-hypertensive drugs, Anti angina drugs, Anti lipidemics, Oral contraceptives, Histamine-2-receptor antagonists.

Table 8: Effect Of Tobacco Consumption On Various Drugs

Phenacetin:-	Much lower plasma levels in smokers compared with non-smokers due to increased metabolism.
Antipyrine:-	Increase in drug clearance.
Testrogens:-	Possible decreased oestrogen effect due to increased increased metabolism.
Tricyclic antidepressants:-	Decreased antidepressant effect due to increased metabolism.
Propanolol:-	Decreased Propranolol effect due to increased metabolism.
Phenylbutazone	Decreased phenylbutazone effect due to increased metabolism.
Mexileline:-	Decreased mexiletine effect due to increased metabolism.
Chlorzoxazone and with caffeine:-	Cigarette smoking accelerates chlorzoxazone and caffeine metabolism by markedly enhancing oral clearance.

Drug Interactions Effecting Excretion Of Drugs:-

The renal excretion of drugs (or their metabolites) may be affected by a co-administered drug in various ways. A change in a glomerular filtration rate; tubular secretion or urinary PH can alter the elimination of some drugs.

4. CONCLUSION

Drug interactions have major role in Therapeutic management of disease. it may produce beneficial or adverse effects based on the type of interactions. Much attention needs to be paid before going to prescribe or taking medication. Enzymatic inhibition & induction also play a role in Drug interaction as they a clinically relevant effect in presence of drugs with a low therapeutic index, a long half-life and a higher bound with plasma proteins.

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Table 9: Interactions affecting excretion of drugs

Interactions affected excretion of drugs	OBJECT DRUG(S)	PRECIPITANT DRUG(S)	INFLUENCE ON OBJECT DRUG
Changes in active tubular secretion	Pencillin,PAS, cephalosporin, nalidixic acid ,dapsone, methotrexate	Probenecid	Elevated plasma levels of acidic drugs: risk of toxic reactions.
	Procainamide	[14]Cimetidine	Increased plasma levels of basic object drugs:risk of toxicity
	Acetohexamide	Phenylbutazone	Increased hypoglycemic effect
	Amphetamine,tetracycline Quinidine	Antacids,thiazides,acetohexamide	Increased passive reabsorption of basic drug,increased toxicity.
Changes in urine pH	Penicillin ,Indomethacin	Probenecid	Reduction in renal clearance of pencillins & indomethacin by coadministration of probenecid
	Methotrexate	Salicylates Nsaids	Reduction of renal clearance
	Digoxin	Amiodarone,quinidine,verapamil,spironolactone	Digoxin excretion can be reduced this will increases its toxicity.
Changes in renal blood flow	Lithium	Nsaids	Decreased renal clearance of lithium risk of toxicity.
Altered clearance	Lidocaine	propranolol	The lower hepatic clearance of lidocaine when given together with propranolol.Propranolol deministes cardiac output and Hence hepatic blood flow; which inturn; reduces the clearance of lidocaine a drug highly extracted by the liver presumably because the degree of adrenergic blockage is a graded response; the interaction with lidocaine is independent on the plasma concentration of propranolol.
	Imipenen	Cilastatin	Imipenem (antibiotic), Imipenem is extensively metabolised in kidney by a dehydropeptidise; located at the brush broader of the proximal tubular cell, consequently the urinary excretion of extent imipenem is low and often insufficient to guarentee effective treatment of urinary tract infections. To improve the efficacy of imipenem it is marketed in the combination with cilastatin;adehydropeptidase inhibitor; which markedly increases the urinary excretion of unchanged imipenem.

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