CHAPTER

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Drug Interactions - Mechanisms and Clinical Implications

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Introduction

Every time a drug is administered with any other prescription medicine, OTC products, herbs or even food we expose ourselves to the risk of a potentially dangerous interaction. Understanding these potential reactions and their mechanisms help us to navigate the hazardous waters of combining drugs with other medicines, food, herbs and vitamins with confidence.

A ***drug interaction*** occurs when the pharmacological effects of the object drug alters the intensity of the precipitant drug. Whenever two or more drugs are taken concurrently there is a chance of an interaction among the drugs that could manifest as an increase or decrease in their effectiveness or an adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome and warrant hospital admissions, ranging upto 3.8%.[1] In our clinical practice there is fast accumulating voluminous evidence of the ever increasing reporting of new drug-drug interactions between a plethora of medications being introduced every day, specially in the elderly with chronic ailments subjected to poly pharmacy for the treatment of a multitude of diseases; thus making it difficult for any physician to remember avoiding potential drug interactions. It is imperative therefore and behoves us clinicians to have the mindset of a detective to piece together unusual experiences that defy logical explanation in patients who are stable on a set regimen and constantly remain vigilant to the possibility of a previously unknown adverse reaction arising in patients under one's care for their safety and well being when two or more drugs are administered concomitantly. Of particular importance in assessing such adverse reactions the first thing that one should be alert to is the recent addition of any new drug to a previously stable regimen that could account for the adverse effect or alteration in the patient's physiological functions in handling the administered drugs compared to a baseline.

Despite all such precautions the ground reality is that the potential for a drug to induce an interaction does not generally surface until it has been widely used in the real world. Therefore our endeavor has to be alert by providing the correct drugs at the right dose to a particular patient who is perforce subjected to polypharmacy. Which is not always an easy task, hence the need to remain well informed and updated.

Interactions should always be considered in the differential diagnosis of any unusual response occurring during drug therapy. Clinicians need to be aware of the fact that patients often see multiple

physicians and come to them with a legacy of drugs acquired during their previous visits and therefore are not always aware of all the patient's medication; necessitating the need to obtain a thorough and meticulous drug history that should include the use of OTC products and health foods.

While it is well nigh impossible to list every conceivable interaction with the currently available drugs or food; some drugs that are most likely to precipitate interactions include those that are highly protein bound such as aspirin or phenylbutazone; drugs that stimulate the metabolism of other drugs such as phenytoin, carbamazepine, rifampicin and griseofulvin; or those that inhibit the metabolism of other drugs which include allopurinol, cimetidine, metronidazole, ketoconazole,chloramphenicol, quinolones and MAO inhibitors and drugs that alter renal elimination like diuretics and probenecid. In general certain groups of drugs, particularly NSAID's, anticoagulants, anti epileptics, oral contraceptives, antibiotics, statins, antipsychotics, drugs enhancing G.I. motility, digoxin and other drugs having a low therapeutic index, pose a daily challenge for practicing physicians.

As automated computer alerts are available for the great plethora of marketed drugs listing all significant interactions, it is not in the purview of this article to list all of them, but with the bewildering array of drug interactions that are surfacing continuously the focus of this article is chiefly to enable a better understanding of the scientific mechanisms of clinically significant drug interactions that occur commonly, in order to provide the right insight to clinicians so as not to lose sight of the more serious drug interactions and their clinical implications. Certain drugs consistently run the risk of generating interactions through well understood mechanisms so when such drugs are started or stopped the prescriber must be alert to the possibility of drug interactions. Their early detection could enable reconsideration of the culprit treatment regimen and prudent management if they do lead to adverse events.

Early evaluation of drug interactions

Despite a general awareness of the problem of drug interactions and widespread efforts to monitor them, the physician fraternity has failed so far in predicting and preventing them. Because drug interactions could not be generally predicted, one had to wait till they appeared in literature. Today we do not have to, as simple pharmacological properties and in-vitro evaluation gives us an index of potential interactions in-vivo.

Recognition of potential interactions should really commence early in the development of new drugs. Appropriately designed pharmacokinetic Phase 1 studies could provide important information about drug metabolism and relevant metabolites and actual or potential drug interactions. Blood levels in Phase II and III could also reveal interactions although the limitations of use of concomitant drugs in these phases may not provide optimal information about drug interactions. This type of in-vitro assessment needs to be done to provide the practicing clinician the potential interactions that could occur when the new molecule is used with older drugs concomitantly to treat specific diseases.

There are now established algorithms suggesting the type of studies that need be done depending on whether the new drug is a substrate or not and whether its metabolic pathway is a major one or not. Sensitive CYP3A substrates refers to drugs whose AUC values have been shown to increase 5 fold or greater when co-administered with a known CYP3A inhibitor. The in-vitro testing of drug interactions can now be conducted using defined, preferable and acceptable substrates approved by the US FDA for testing various CYP 450 isoforms in order to get a predictive insight unto why and how certain drugs interact, much before larger human use of the new drug. As an example CYP3A4 metabolises cyclosporin and it is known that rifampicin is an inducer of this enzyme while ketoconazole is an inhibitor, hence it becomes obvious that rifampicin would reduce cyclosporin levels (that could lead to

transplant rejection;[2] while the latter would increase it five to ten fold.[3]

However in-vitro data does not exactly translate always in the clinical scenario, because of immense variables that come in to play. Some drugs can be metabolized by more than one enzyme whereas some others like carbamazepine can not only induce a particular isoenzyme (CYP3A4) but also gets metabolized by it necessitating gradual dosing, while a few others can inhibit a particular isoenzyme but not be metabolized by it.

While it is therefore tempting to suggest that in vitro testing can prospectively rather than retrospectively indicate which other drugs may probably interact, the ground reality is slightly different due to the compounding factors impinging on the outcome; hence it is not so simple to think that we can get all answers this way.

Magnitude of the problem

Drug interactions are complex and chiefly unpredictable as a known interaction may not occur in every individual taking the drug or even a drug in the same class. The exact incidence of drug interactions in real life situations is largely unknown because a fair number do not get reported, do not result in any substantial harm to patients or may not end in hospitalization and even when it does it gets recorded as an adverse reaction rather than a drug interaction. While significant drug interactions for commonly used drugs are recognized, there is a tendency amongst the fraternity to disregard the magnitude of evidence that potential interactions can manifest with the use of many of the drugs prescribed today.

There is a common assumption that all drug classes have a homogenous interaction potential when this is actually rare. This assumption may have had some credence when the number in a particular class was small and the mechanism of action was uncertain but with increasing knowledge about the mechanisms, this myth has been disproved. For example, amongst the macrolide class, while erythromycin and clarithromycin inhibit CYP3A4 leading to interactions with other drugs, Azithromycin does not. Likewise while ketoconazole interacts with lovastatin and simvastatin and raises their plasma levels it does not do so with rosuvastatin[4] or pravastatin.

The large inter-patient variability in the magnitude of the effect makes predicting the clinical outcome of an interaction nearly impossible as 5-7 fold differences in effect between participants is observed. However the inherent possibility of a drug interaction is intensified with the increasing use of a multitude of drugs by different routes in various doses and formulations administered concomitantly by doctors in clinics and hospitals specially to as many as 80% of elderly patients with serious chronic ailments, more so in I.C.U settings. The matter is often compounded by patients additionally taking OTC drugs that interact with their prescribed medication about which the doctor may not know; with other modifiers of drug elimination and response and genetics.

The magnitude of the problem can be gauged by the U.S Institute of Medicine's report[5] that medication errors were a major source of medical errors, with a 1999 estimate revealing 44000-98000 persons dying due to medical errors. A retrospective cross sectional analytical study of 46 million patients revealed that 374000 had been exposed to 25 potential dangerous drug interactions of clinical importance.

Sloan[6] has pointed out that when 2 drugs are used in combination the interaction potential is 5-6%, that goes upto 50% with 5 drugs and when 8 drugs or more are co-prescribed the potential may even reach 100%. Earlier screening of 1800 records in a surgical setting[7] revealed an incidence of 17% and a nursing home study[8] showed an incidence of 19% and in a medical setting[9] 22% interactions. Another early study[10] reported an incidence of 7% when 6-10 drugs were prescribed that rose to 40% when 15-20 drugs were given.

The earlier studies merely recorded the adverse events theoretically without realizing their clinical significance but the later studies however avoided this error by only considering potentially clinically important interactions, such as the Boston Collaborative surveillance study[11] that involved 9900 patients with 83000 exposures, and reported that 234 (6%) of ADR's were due to drug interactions and three other studies[12,13,14] that reported an incidence of 4.1%, 2.9% and 1.9% of clinically important interactions respectively.

These reports reveal a discordant note but not withstanding this skepticism we need to ensure that there is no under reporting and the physician needs to be alert to the possibility of the occurrence of certain potential interactions of clinical importance. Clearly drug interactions present a health risk to patients and a great challenge to the physician as monitoring the patient's therapy is a standard of care expected by the patients and the liability of interactions rests squarely on the physician who fails to recognize potentially harmful interactions to avoid extra costs of healthcare.

How do drug interactions occur

There are various categories of interaction with drugs:

- Drug- Disease interactions
- Drug-Drug interactions
- Drug- Food interactions
- Drug- Herb interactions
- Drug Environmental interactions

Knowledge of the mechanism by which a given drug interaction occurs is often useful in practice, as the mechanism could influence both the time course and methods of evading the interaction.

It is therefore incumbent upon the physician to be familiar with the basic principles of drug interactions in planning a therapeutic regimen as there are several factors affecting the likelihood of a known interaction such as age, sex, lifestyle, physiological differences, time and sequence of administration and genetic polymorphisms in some of the main CYP isoforms notably CYP2D6 and CYP3A4 that affect enzyme function. Further, as the number of drugs prescribed increases especially in the elderly, so does the susceptibility to drug interactions specially in the absence of an accurate drug history and a lack of knowledge of potential consequences.

Because of the complexity of pharmacotherapy needed for the treatment of the basic disease, its underlying causative factors, its complications and accompanying co-morbid conditions such as hypertension, diabetes and dyslipidemia, malignancy and respiratory disorders, the number of drugs prescribed increases translating into a major risk factor for potential drug interactions. Diseases apart, physiological changes in renal and hepatic function with advancing age, malnutrition and reduced homeostatic mechanisms makes the elderly more sensitive to the additive effects of two or more drugs rendering them more prone to serious drug interactions. The objectives of treatment are therefore vital while assessing the clinical implication of a drug interaction as a balance needs to be struck between increased toxicity and reduced efficacy.

An understanding therefore of the classification and mechanisms of drug interactions is essential in order to predict their occurrence and comprehend their clinical significance and is the only way a clinician can be prepared to analyze new findings systematically; as there are certain mechanisms that are encountered repeatedly but a few others are unique and many drugs that interact do so not necessarily by a single mechanism but quite often by two or more mechanisms in consonance with each other.

Drug-Drug interactions

Although tremendous advances have occurred in our understanding of the mechanisms of drug interactions over the last few years we still have a long way to go to understand them fully as more than one mechanism may play a part in some drug interactions.

Knowledge of the mechanism by which a given drug interaction occurs is often clinically useful, since the mechanism may influence both the time course and methods of circumventing the interaction.

The etiology and clinical implications of drug-drug interactions are multifactorial and chiefly unpredictable, that include patient as well as drug factors alluded to earlier.

Drug- drug interactions reflect the modulation of the pharmacological activity of the object drug by concomitantly administering the precipitant drug resulting in a severe decrease or increase in the pharmacological properties of either drug.

The clinically most important adverse drug-drug interactions occur with drugs that have easily recognizable toxicity and a low therapeutic index, such that relatively small changes in drug effect can have clinically significant adverse consequences. Another dimension of drug-drug interactions that could have clinical significance is the seriousness of the disease that is being treated, which if left untreated could be fatal.

There are several mechanisms by which drugs may interact but most can be classified as:

- Pharmacokinetic Interactions
- Pharmacodynamic Interactions
- Additive or Synergistic Interactions
- Antagonistic or Opposition interactions

Major adverse drug interactions ordinarily do not result from the "additive" effects of drugs acting at the same receptor site or from pharmacological or physiological antagonism as their combined effects can easily be predicted from their known pharmacology. Adverse drug interactions resulting from concomitant medication are commonly associated with drugs that are chemically or biochemically antagonistic.

Thus the mechanisms usually responsible for adverse effects associated with drug interactions are those in which one drug affects the pharmacokinetic profile of absorption, distribution, metabolic biotransformation, excretion or elimination of another; or pharmacodynamic, such as interactions between agonists and antagonists at drug receptors, leading to vastly altered clinical response and implications.

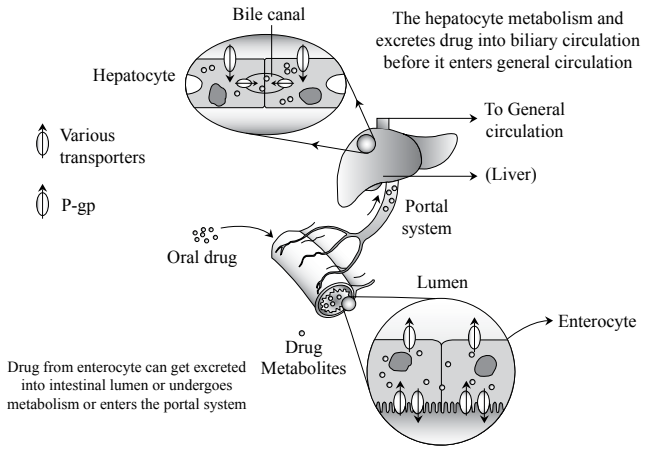
Pharmacokinetic Interactions

The science of therapeutics does not merely involve testing of new molecules in animals and humans, but applies more importantly to the treatment of each patient holistically as an individual and it is widely recognized that individuals show wide variability in response to the same treatment.

Pharmacokinetic interactions must always be evaluated in the context of their clinical relevance. The fact that two drugs share a common metabolic pathway does not mean they will have a clinically significant interaction when co-administered; the interaction being dependent upon various factors including relative affinities of each drug for the binding site or the metabolising enzyme; as well as the effective free drug concentration available for binding. Moreover parallel pathways for elimination of one or both drugs would tend to reduce the potential for a significant pharmacokinetic interaction.

Hence, to avoid interactions; inter and intrapatient variations in disposition of a drug must be taken into consideration in choosing a treatment regime, such as the prescribed dose and its compliance, the actually administered dose, its rate and extent of absorption, plasma concentration, Tmax, AUC, distribution, metabolism, the rate of elimination (t1/2), drug concentration at the site of action, genetic variations and the effect of the drug at the receptor. The major determinants of the disposition of many drugs are the physiological and pathological variations in organ function. In general, pharmacokinetic interactions are considered clinically significant when at least a 30% change is seen in Cmax, Tmax and AUC.

Figure 1



Pharmacokinetic interactions occur when the absorption, distribution, metabolism or elimination processes of the object drug is altered by the precipitant drug.

Drug absorption interactions

Since the oral route is the one most frequently used to administer drugs, interactions influencing absorption are more likely to occur within the gastrointestinal tract, which more often result in reduced rather than increased absorption.

While the absorption of a drug may be altered by another, the resulting interactions are of varying clinical importance as we need to make a definitive distinction between drugs that influence the rate of absorption as opposed to those alter the extent of absorption as the rate is more often unimportant in case of chronically administered drugs such as warfarin provided the extent is not markedly altered, while it is a different scenario when an analgesic is given where a high concentration may be needed rapidly to achieve an adequate effect when the interaction becomes clinically important if it results in subtherapeutic serum levels of the various possible interactions that occur due to alterations in drug absorption most clinically significant interactions occur due to the following factors:

Changes in gastrointestinal pH

Absorption in the gut is governed by the gut pH, lipid solubility and pKa of the drug, and action of the P-glycoprotein. While changes in gastric pH induced by H2 and proton pump blockers and antacids containing Al/Mg formulations have been shown to significantly reduce drug bioavailability;[15] in clinical practice the outcome is a bit uncertain due to other compounding factors such as chelation and gastric motility. However the alteration in pH has certain clinical implications as it can result in a significant reduction in the absorption of ketoconazole and itraconazole which are insoluble in water and are only ionized at low pH, hence gastric acidity plays an important part in this interaction. Likewise salicylic acid absorption is greater at low pH.

The absorption of quinolones are also reduced when given along with antacids. Other drugs that are influenced by changes in pH are glipizide, glyburide, cefuroxime and cefpodoxime.

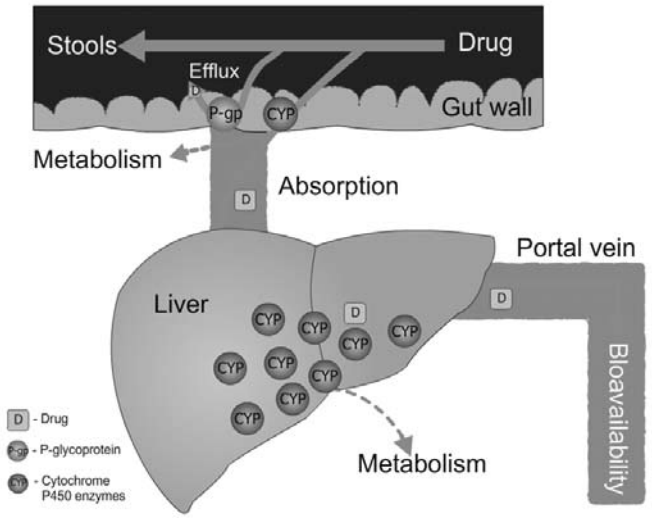
Changes induced by chelation and adsorption

Of the various possible drug interactions that occur due to alterations in drug absorption the most clinically significant interactions occur due to chelation or formation of insoluble complexes or when drugs are bound to resins that bind to bile acids.

Clinically important interactions relate to use of tetracyclines as well as ciprofloxacin that can form insoluble chelates with Ca, Al, Bi and iron, resulting in its reduced antibacterial effects. This interaction can however be avoided if the interval between the medications is at least 2-3 hours. Chelation also seems to play an important part in reducing the bioavailability of penicillamine caused by some antacids.

The commonly used Kaolin-pectin suspensions in diarrheal disorders bind digoxin, when co-administered reducing its absorption by 30-50%, while resins like cholestyramine and colestipol that

Figure 2



sequester bile acids in the gut bind to a number of drugs like digoxin, levothyroxine, statins, valproic acid, steroids, loop diuretics and warfarin reducing their absorption with resultant clinical implications warranting close clinical and biochemical monitoring to avoid complications. Further estrogen metabolites in bile are deconjugated by bowel organisms and reabsorbed and if this is prevented by poorly absorbed antibiotics such as ampicillin the contraceptive effect gets reduced with a risk of pregnancy. Antibiotics that alter gastrointestinal flora can reduce the rate of synthesis of vitamin K with a resultant increase in the effect of oral anticoagulants due to a competitive mechanism between them. Dilantin was reported early on to inhibit an intestinal conjugase which was found to inhibit the absorption of folic acid specially in susceptible individuals.[16, 17]

Changes in gastrointestinal motility

Drugs that alter the stomach-emptying rate can affect the rate of absorption of drugs as most of them are absorbed in the small intestine. Drugs with anticholinergic properties like propantheline or those altering bowel motility like diphenoxylate may affect the absorption of other drugs. Propantheline increases the absorption of slow dissolving Digoxin by 30% as the reduced gut motility allows a slow dissolving Digoxin formulation more time to pass into solution making a greater amount available for absorption but this effect is not seen with fast dissolving tablets. Metoclopramide on the other hand produces the opposite effects on motility and digoxin absorption.[18]

It may also be pertinent to point that the ultimate outcome of interactions of drugs exhibiting anticholinergic properties that decrease gut motility like tricyclic anti-depressants can be unpredictable due to several mechanisms because on one hand they may reduce the absorption of a drug like levodopa as the exposure time to intestinal mucosal metabolism is increased; while on the other they increase the absorption of dicoumarol possibly by increasing the time available for its dissolution and absorption, although the exact mechanism is not understood clearly.

Transporter based interactions

Uptake into the enterocyte particularly by the active processes is mediated by specific drug uptake transport molecules. Once the drug enters the enterocyte it could enter the portal circulation, undergo metabolism or it may get excreted back into the intestinal lumen resulting in decreased systemic bioavailability (Fig. 2).

Transporter based interactions have of late been recognized much more than earlier and arise chiefly due to the induction or inhibition of many identified transporter proteins rather than due to other mechanisms earlier attributed to protein displacement or enzyme inhibition or induction.

Two mechanisms are important modulators of presystemic clearance of some drugs. The first one that has a greater clinical relevance and perhaps best studied is P-glycoprotein (P-gp) which is a product of the normal expression of the MDR1 gene and is expressed on the apical aspect of the enterocyte as well as on the canalicular aspect of the hepatocyte, works as a ' detoxification' pump ejecting drugs that have diffused across the intestinal epithelial barrier resulting in a reduction of the drug absorbed and

greatly influences the oral bioavailability of some drugs. The second is intestinal metabolism of drugs such as anti-fungals by theCYP3A4 enzyme. Other transporter proteins are OAT, OATP, OCT, MRP, BCRP, ABC-ATP, and SLC. Induction or inhibition of these proteins also leads to drug interactions. Of these OAT is inhibited by probenecid that influences the excretion of a number of drugs.

Examples of transporter based interactions include digoxin with quinidine, rifampicin or verapamil; and fexofenadine with ketoconazole; penicillin and probenecid. Digoxin is not extensively metabolized but it is transported by the efflux pump P-gp that is expressed in excretory tissues, kidney, liver and intestine. Rifampicin induces P-gp activity in the gut lining thereby ejecting digoxin into the gut[19] with resultant falls in its plasma levels; on the other hand Verapamil inhibits P-gp activity and raises Digoxin levels.

Fexofenadine, Quinidine and digoxin are substrates for P-gp and quinidine is a potent inhibitor of digoxin transport. The interaction between quinidine and digoxin is of definite clinical importance and is well documented. There is evidence that P-gp inhibition by quinidine may play an important part in the absorption of digoxin in the small intestine[20, 21] leading to increased plasma digoxin levels. Quinidine is known to increase digoxin levels perhaps by reducing renal excretion by 40-50%[22] but the exact mechanisms are not clear as there is also a biliary as well as an intestinal component of excretion.[23]

Activity of P-gp in the endothelial cells of the blood brain barrier also limits distribution of drugs into brain limiting CNS penetration. Of some clinical importance is the fact that P-gp inhibitors could increase the uptake of drug substrates into the brain which could either increase the CNS adverse interactions or even be beneficial, by inhibiting P-gp activity, ketoconazole has been shown to increase the levels of ritonavir in the CSF.

Drug distribution interactions

Many drugs interact by displacement of each others binding to plasma proteins. Acidic drugs are known to have an affinity to bind to plasma proteins, hence when two or more are given concomitantly, competitive binding for the same site or receptor may displace one drug from the protein binding site increasing the amount of the displaced free drug in plasma and various tissues setting up an interaction leading to an enhanced potential for toxicity, such as is seen in the case of concomitant administration of warfarin with phenylbutazone or other highly protein bound drugs that leads to increased levels of warfarin, with the clinical implication of frequent monitoring of INR and PT to prevent bleeding.

Another factor that influences this type of interaction is hypoalbuminemia as patients manifesting this condition will have more free or active drug available.[31]

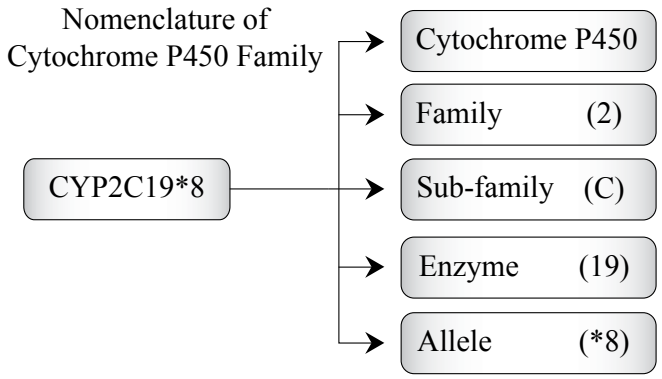
The drugs most likely to lead to clinically significant interactions are those that are: 90% or more protein bound, those bound to tissues or having a small volume of distribution, having a low therapeutic index, low hepatic extraction ratios, or those that are administered I.V.[24]

Drugs that are more likely to displace other drugs from protein binding sites include NSAID's, phenylbutazone, salicylic acid, and sulfonamides.

Drugs may involve displacement of a drug not only from plasma protein binding sites but also from tissue binding sites. Examples of drugs displaced from receptor sites leading to clinically significant interactions include Quinidine displacing digoxin from skeletal muscle sites thereby increasing digoxin levels leading to toxicity. However this interaction and others involving highly protein bound drugs is a complex one that also involves other mechanisms like induction or inhibition of metabolism.

Drug interactions involving alterations in distribution because of volume changes is exemplified by the combined use of gentamycin and frusemide. As gentamycin is well distributed

Figure 3



in extracellular fluid any reduction in ECF induced by frusemide reduces the volume of distribution of gentamycin increasing its serum levels with the clinical implication of nephro and ototoxicity.

Despite the factors described above for distribution interactions, recent research[25] suggests that although in-vitro many commonly used drugs are capable of being displaced by others, in the body these effects seem almost always so well buffered that the outcome may not normally be clinically important. Moreover, as some interactions assumed to be originally due to protein binding have subsequently been shown to have other mechanisms involved it has been suggested that the importance of this mechanism alone being responsible for the interaction has been exaggerated. This however does not deter from the fact that cognizance of alterations in protein binding is invaluable for therapeutic drug monitoring.

Drug metabolism interactions

In a monograph on clinically significant drug interactions, metabolic interactions are most important and need to be examined in great detail. Recent scientific developments, particularly in the area of the CYP450 enzymes have revolutionized the study of drug interactions resulting in a deluge of published drug interactions that has bewildered the practicing physicians.

The human body is continuously exposed to foreign substances (drugs) not found naturally in the body that modulate the body function to achieve a therapeutic end that are modified by a plethora of enzymes. As is well known, the processes by which the enzymes alter an active drug inside the body to an inactive one or into active or toxic metabolites are referred to as **drug metabolism or biotransformation.**

Most drugs need to reach a receptor site in order to exert their systemic effect and need to be lipid soluble so as to be able to penetrate the lipid plasma membrane barrier. The lipid soluble drugs further need to be converted into a water soluble form to be excreted chiefly by the renal route and the chief role of metabolism is to enable these processes in two phases.

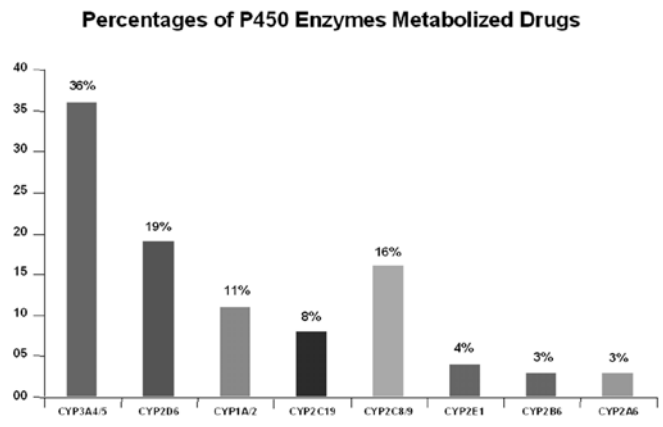
In phase I, **oxidation/reduction reactions** convert the drugs into a more polar form, while Phase II reactions provide another set of mechanisms involving conjugation / hydrolysis with substances like glucuronic acid and glucuronyl transferase for modifying drugs into inactive compounds to enable their excretion.

Phase I reactions are catalysed by a family of mixed function oxygenases called the "**Cytochrome P 450**" class, expressed chiefly within the microsomal smooth endoplasmic reticulum hepatocytes and to a lesser extent in other cells.

The nomenclature for this class of enzyme is usually abbreviated to 'CYP" followed by an Arabic number indicating the enzyme family and a capital letter to indicate the enzyme sub family and then an additional number to describe the specific enzyme e.g. CYP2D6. Allelic forms are described with an * and a number or number letter. This enzyme complex is so named because it is bound to a membrane within a cell (**C**yto) and contains a hem **P**igment (chrome and P) that absorbs light at a wave length of 450 nm when exposed to Co2. The net result is "**Cytochrome P 450".**

The interaction starts with the drug binding to the oxidized (Fe) CYP450 complex which is then reduced in two oxygenation/reduction steps using a reactive hem ring with an iron atom on the ultimate electron acceptor donor and NADPH as a necessary

Figure 4



co-factor.

The CYP450 complex is essential for metabolism of drugs and interactions mediated by it and what is significant is that out of 50 enzymes in this class, each encoded by a different gene, just 6 of them (CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5) together account for 90-95% of biotransformations; with the 3A4 and 2D6 sub families being responsible for a large number of clinically important interactions.[26]

However, there is a considerable variability in enzyme activity between patients due to medical, environmental, nutritional and genetic polymorphisms reasons with polymorphism being specially significant for CYP2D6, CYP2C9, and CYP2C19 and CYP3A4.[27]

A drug's action on a molecular target already results in a biological complex that could be influenced further by disease. On top of this genetic polymorphisms that influence change in this biological complex can greatly influence drug response. In this context, while 20% of Asians are poor metabolisers of drugs dependent on CYP2C19 metabolism such as phenytoin, omeprazole[28] phenobarbitone and other drugs; only 2% of the same population exhibits a variant of CYP2D6 with low activity. These differences in the variability to metabolise different drugs could account for a few persons manifesting toxicity with interacting drugs while others do not exhibit any symptoms.

The clinical implication of this polymorphism is exemplified by omeprazole, where poor metabolisers having higher drug levels with standard dosages had markedly higher cure rates (100)% than their EM counterparts; highlighting as well the need for identification of such polymorphisms early in a drug's development. The I/D deletion polymorphism in the ACE gene, G6PD deficiency gene and the ABCA1 transporter gene in addition can all result in clinically important adverse interactions of which physicians need to be cognizant.

Phase II **conjugation/hydrolysis** reactions provide a second set of mechanisms for modifying compounds for excretion wherein large water soluble metabolites are acted upon by non P450 enzymes such as N-acetyl and glucuronyl transferase systems which render them inactive or less active water soluble metabolites.

Clinically significant interactions however, are caused chiefly by Phase I reactions as most of the metabolism occurs in the liver via the P450 enzymes, rather than phase II metabolism. Although significant metabolism takes place in the liver, other organs like the kidney and gut are also involved. During the first passage through the liver, certain drugs are extremely metabolized and are referred to as high extraction drugs. These drugs having a short half life and inactive metabolites are clinically less affected by interactions than their low extraction counterparts. However, lower the therapeutic index of a drug, it has a greater clinical potential to produce more serious consequences of drug interactions affecting metabolism.

Crucial to the ability to predict drug interactions is a proper understanding of drugs influencing CYP 450 enzyme induction and inhibition. Interactions involving drug metabolism can increase or decrease the amount of drug available for action by **inhibition or induction of metabolism.** Inhibition is usually more predictable than induction which is influenced by genetic differences between patients.

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug, that then accumulates in the body resulting in toxicity.

Strong inhibitors achieve a 5 fold increase in plasma AUC or an 80% decrease in clearance, while moderate inhibitors lead to a 2 fold increase in AUC and 50-80% decrease in clearance of the substrate drug.

Inducers, on the other hand stimulate the production of the CYP isoform, thus increasing the rate of metabolism and enabling substrate drug to clear out of the system faster. This decreases its response, rendering the drug ineffective, as it does not remain in the system long enough. Enzyme induction does not occur quickly, usually taking a week or two as its maximal effect depends on enzyme synthesis and t1/2 of the inducing drug, which in the case of phenobarbitone may require a longer time, while rifampicin with its short t1/2 can manifest its effects within 24 hours.

Conversely inhibition of CYP enzymes tends to be rapid with maximum effect occurring when steady state concentrations of the inhibitor drug are established. However if the t1/2 of the affected drug is long it may take a week to reach steady state levels. This inhibition leads to decreased metabolism of drugs acted upon by the enzyme, prolonging its t1/2 and reducing clearance, thereby increasing plasma levels that lead to interactions.

Investigating the likelihood of CYP mediated interactions in a multicenter audit of patients attending daycare centers, Wilcock[29] categorized drug interactions as either "clinically important" for which there is in-vitro metabolic and in-vivo clinical evidence or "potentially clinically important" if there was a theoretical but not experimental basis and "unlikely" if there is no real basis for interaction. Audited prescriptions of 160 patients revealed a median of 7 drugs co-administered, with 77% of patients having received a median of 4 drugs that were either substrates, inducers or inhibitors of the CYP450 enzyme system. 24 combinations of drugs administered induced "*clinically important" or: potentially clinically important"* interactions involving CYP 450 enzymes in 20% of patients. Of these, 2 important interactions reported were, one with a diazepam/omeprazole combination due to CYP inhibition, causing increased diazepam concentrations resulting in drowsiness and the other involving a phenytoin-dexamethasone combination that led to decreased dexamethasone concentrations due to CYP inhibition. Of the potentially important interactions, 50% were associated with steroids given together with amlodipine or simvastatin or trazodone or amitryptiline and 25% with analgesics.

Effects of enzyme inhibition on drug metabolism

The extent of inhibition of metabolism of a drug depends in fact on the dose and binding ability to the enzyme. Potent inhibitors of an enzyme that may not even be its substrate have the greatest potential for interactions requiring the physician to be specially alert to them. Clinically relevant interactions of inhibited drug metabolism occurring through oxidative processes include inhibition of warfarin metabolism by phenylbutazone, cimetidine, chloramphenicol, and metronidazole; inhibition of theophylline metabolism by quinolones and macrolides and inhibition of phenytoin by isoniazid resulting in increased therapeutic levels and toxicity. CYP1A2 inhibitors can increase the risk of toxicity from theophylline or clozapine; CYP2C9 that of phenytoin and warfarin; while CYP3A4 inhibition results in the hazards of toxicity of a larger number of drugs like carbamazepine, lovastatin and simvastatin, rifabutin, cisapride, cyclosporin, ergot, protease inhibitors and vinca alkaloids.

Pro-drugs require enzyme activation to produce their effect, hence enzyme inhibition results in a reduced activity of the drug. The analgesic effect of codeine results from its conversion to morphine by CYP2D6, hence its inhibition decreases codeine's therapeutic effect.

Figure 5

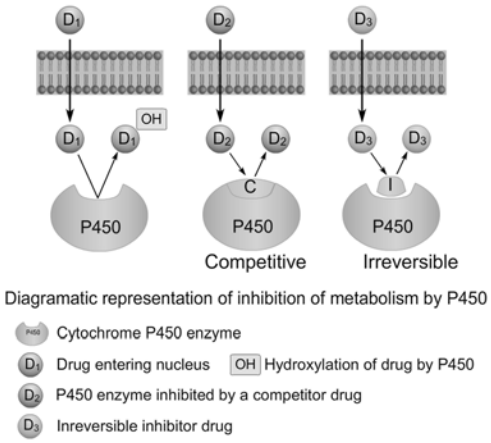
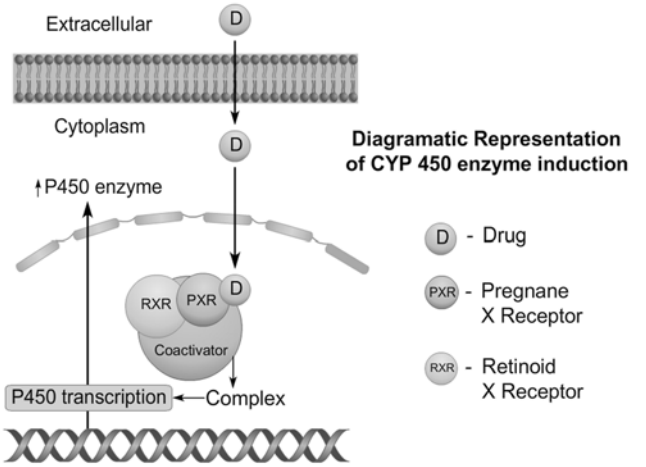


Figure 6



Other inhibitory interactions utilizing different pathways include Azathioprine and 6MP that are metabolized by Xanthine oxidase, which is inhibited by allopurinol and the interaction of MAO inhibitors with tyramine rich products such as cheese that precipitate hypertension.

Inhibition of enzymes can occur in different ways such as is seen with ketoconazole, whose nitrogen moiety binds to the heme iron in the P450 enzyme site preventing the metabolism of concomitantly administered drugs either by competitive or irreversible inhibition that is achieved for instance by secobarbital that alkylates and inactivates the P 450 enzyme permanently (Fig. 5)

P450 inhibitory interactions can also occasionally be therapeutically useful as in the case of lopinavir whose drug concentrations are actually increased by the co-administration of the CYP3A4 inhibitor ritonavir, since the first-pass metabolism of the former precludes it achieving therapeutic levels on its own.

Effects of enzyme induction on drug metabolism

While some P450 enzymes are active constitutively other enzymes can be induced by different drugs. Induction of CYP isoenzymes is achieved slowly by drugs like rifampicin, phenytoin, carbamazepine, barbiturates, glutethemide, troglitazone, rifabutin, griseofulvin and St John's Wort, by increasing the amount of endoplasmic reticulum in liver cells and by increasing the content of CYP450.Administration of these drugs increases the expression of genes such as MDRI over a fortnight and results in clinically significant interactions by decreasing the plasma levels of co-administered drugs such as warfarin, ketoconazole, itraconazole, quinidine, verapamil, mexiletine, low dose oral contraceptives, prednisolone and theophylline.

The process of P450 enzyme induction gets initiated by an increase in the expression of the enzyme chiefly via increased transcription or decreased degradation. Drugs or food gets bound to and activates several xenobiotic receptors e.g the Pregnane X receptor after entering the liver cells, which then heterodimerises with the Retinoid X receptor (RXR) to form a complex with coactivators to initiate transcription of the P450 enzyme. (Fig. 6)

Drugs metabolized by CYP2C9 and CYP3A4 are particularly susceptible to enzyme induction.

The reduction in the plasma levels of the object drugs brought about by inducers leads to a reduction in their clinical effects, that could lead an epileptic to manifest fits while on phenytoin or a pregnancy resulting while on oral contraceptives.

Ritonavir is an example of a drug that not only induces but also acts an inhibitor of the isoenzyme CYP D6 depending on the situation.

Enzyme inducing drugs can also increase the activity of phase II metabolism processes such as glucuronidation. Once the drugs responsible for induction are stopped their effects take an equally long time to disappear and this can result in major toxicity if the dose of a low therapeutic index co-administered drug that has been stabilized in the presence of an inducer is suddenly stopped; such as is seen in the case of warfarin, digoxin etc.

Some drugs are converted to toxic metabolites by enzymes and enzyme inducers can increase the formation of these toxic metabolites. Paracetamol is primarily converted to nontoxic metabolites but a small amount is converted to toxic metabolites; however if administered with an enzyme inducer it could lead to hepato-toxicity.

Drug elimination reactions

The major routes for elimination of drugs remain the kidney and bile, but there are no significant drug - drug interactions through bile elimination, but only drug-disease ones.

Drugs that are chiefly excreted by the kidneys can get involved in drug interactions by different mechanisms such as **Competition at active transport sites, or** alterations in **Glomerular Filtration, passive renal tubular reabsorption or active secretion and urinary pH.**

Active secretion into the renal tubules is an important excretion pathway for some drugs, that gets affected by the co-administration of certain other drugs, thereby affecting their therapeutic response. The capacity of a drug to inhibit the renal excretion of another is dependent on an interaction at active transport sites. The beneficial probenecid - penicillin/amoxycillin interaction exemplifies one of the many reported interactions at the anion transport site; the two drugs competing for excretion by modifying active transport in the renal tubules resulting in probenecid being excreted and the antibiotics being retained and reabsorbed, with the clinical implication of increasing their plasma levels to a desirable level to increase its therapeutic effect and prolonging the plasma t1/2.

However adverse interactions are seen with concomitant administration of digoxin with drugs like quinidine, verapamil and amiodarone, leading to digoxin toxicity.

The interaction between quinidine and digoxin is of definite clinical importance and is extremely well documented, resulting not only from quinidine reducing the renal excretion of digoxin by 50%, but also by non renal mechanisms, that includes reduction of about 50% in digoxin excretion in bile[23] as well as by its P-gp mediated inhibition of transcellular transport[30] and also inhibition in the gut.[20] Further, salicylates have been shown to reduce the renal clearance of methotrexate leading to its toxicity. The other interaction involves the excretion of lithium which gets altered by diuretics and NSAID's that inhibit renal tubular reabsorption leading to compensatory reabsorption of lithium with consequent toxicity,

Likewise, interactions at the caution transport site for basic drugs result from drugs like cimetidine, amiodarone and dofetelide inhibiting the excretion of procainamide. Cimetidine also competes with metformin, (both being cationic drugs) for elimination by renal tubular secretion.

The rate of excretion of a drug or its metabolites can be influenced by other drugs that increase or decrease glomerular filtration due to changes in renal blood flow. For drugs with a low therapeutic index like digoxin, phenytoin and warfarin, any increase in renal clearance decreases their steady state plasma concentrations and conversely any reduction in their renal excretion increases circulating levels of the drugs resulting in toxicity.

Finally changes in the pH of urine that alter the excretion of weakly acidic or basic drugs can lead to interactions by affecting their ionization and consequently affecting the reabsorption of drugs that are subject to passive reabsorption from renal tubules. The implication of this mechanism is reflected in the treatment of salicylate or amphetamine poisoning by alkalinising with

antacids or acidifying the urine respectively. Ascorbic acid and other acidifying drugs can result in increasing phenobarbitone levels.

Pharmacodynamic interactions

Pharmacodynamic interactions are relatively common in practice and occur when a precipitant drug alters the clinical effects of the object drug at its site of action. One drug may alter the normal physiological environment whereby it can increase or decrease the effects of another drug as is exemplified by the interaction produced by diuretic induced hypokalemia with the concurrent use of digoxin that results in digoxin toxicity. In a similar situation of diuretic usage concurrently with anti-arrhythmics like quinidine or sotalol a much more serious toxicity in the form of Torsade de pointes can occur resulting in fatal ventricular arrhythmias.

When drugs with pharmacologically similar actions or same active ingredients are concomitantly administered, it invariably results in a synergistic or additive response. The two drugs may or may not act on the same receptor to produce these effects and the effect is one of duplication where the clinical effect is intensified. There are numerous examples of such a response one of which is seen when a cold remedy and a pain reliever (both containing paracetamol) are taken together. Likewise the simultaneous use of two nephrotoxic drugs can aggravate renal damage, where the dose of either drug may have been insufficient to produce toxicity. Amphotericin and pentamidine administered concomitantly result in nephrotoxicity Gancyclovir and Zidovudine given together increase the risk of bone marrow depression. The simultaneous prescription of potassium supplements to patients already on spironolactone or triamtrene and those on ACE inhibitors leads frequently to severe hyperkalemia.

Beneficial interactions of drugs acting at different sites are seen with the combined use of certain antibiotics in treating infections or combinations of cytotoxics in management of malignancies.

Drugs with opposing or antagonistic pharmacodynamic effects reduce response to either drug. NSAID's specially the Cox-2 inhibitors that would normally increase blood pressure tend to inhibit the hypotensive action of diuretics, ACEI's and beta blockers. While the effects of benzodiazepines get inhibited with the concurrent administration of theophylline. However, a few antagonistic reactions can actually be beneficial such as the reversal of the effects of opium alkaloids with naloxone.

Certain pharmacodynamic interactions occur indirectly wherein the toxic or therapeutic effects of either drug are not related directly and seem to act on separate parts of a common process; e.g. warfarin could be involved in an indirect interaction with aspirin when other drugs such as dipyridamole, salicylates or phenylbutazone reduce platelet aggregation or in cases of thrombocytopenia. NSAID's can cause gastric ulcer and patients having concomitant warfarin therapy run a risk of greatly increased bleeding.

Drug - Disease interactions

Drug - disease interactions tend to occur when a medication has the potential to worsen a disease. The effect a drug has in certain patients may be unexpected not related to the drug per se but because of the patient's disease pattern. It is important for the physician to know the patients entire disease profile to plan a suitable therapeutic regimen to avoid drug interactions carefully balancing the need to ensure that the patient is given appropriate medicines to cover his ailments, yet at the same time selecting such drugs from various therapeutic categories that do not or have a lesser potential for inducing drug interactions. This has to be viewed in the context that the patient sub-population prone to interactions are either frail elderly hospitalized patients or critically ill patients or those having chronic diseases.

Certain drugs are capable of exacerbating acute and chronic diseases. e.g. beta blockers are known to precipitate asthma, C.O.P.D. and peripheral

vascular disease[29,30] and can also blunt the signs of hypoglycemia. Certain beta blockers and the calcium blocker verapamil by virtue of their negative inotropic and chronotropic effects have the potential to precipitate C.H.F.

Drug interactions that occur in patients with milder forms of disease and minor clinical significance assume greater significance in patients with more severe forms of diseases such as diabetes, cardiac disorders, asthma, epilepsy, hypothyroidism and liver diseases.

The risk associated with the potential for interactions with the treatment required for certain diseases like psychiatric disorders autoimmune disorders, G.I. diseases, respiratory and infections always poses a problem.

Treatment for diseases involving drugs having a narrow therapeutic window, like digoxin, lithium, phenytoin, warfarin, quinidine and theophylline, poses clinically significant possibilities of predisposition to drug interactions.

Drug - food / nutrients interactions

The myth that natural products, not being drugs, are completely safe creates a need for responsible, public/physician education specially as they are widely used by our rural/semi-urban populace; hence the need to be cognizant of these interactions and as a large number do not inform the physicians about their intake, the potential and true incidence of these interactions is largely unknown. A lack of standardization and contamination further contribute to these interactions. The mechanisms of food-induced interactions are essentially the same as that of drug interactions, however these occur chiefly due to alterations in absorption that may impair their nutritional benefit and to some extent due to altered metabolism.

The common natural products interactions with drugs are due to St John's Wort, ginseng, glucosaminesulfate, ginko biloba, aloe, guargum, senna, grapefruit juice, garlic, fenugreek, tyramine rich foods and curcumin.

St John's Wort is one herb that is responsible for having interactions with many drugs. It reduces absorption of digoxin, lowering its blood levels; amplifies action of clopidogrel increasing risk of bleeding. It has synergistic effects with SSRI's and Zolpidem, increasing serotonin levels in brain leading to "Serotonin Syndrome" By enhancing expression of intestinal P-gp and CYP3A4 it impairs absorption and stimulates metabolism of cyclosporin, resulting in sub-therapeutic levels. Interaction with estrogen results in bleeding and interacting with indinavir, lowers its plasma levels and efficacy, worsening infection. It also lowers warfarin plasma levels and increases clot formation.

It also interacts with the anticancer drugs docetaxel and irinotecan by similar metabolic mechanisms, resulting in larger inactive metabolites and less of the active SN38 metabolite of irinotecan, resulting in lower efficacy. As many cancer patients use alternative medicines with their chemotherapy, unexpected toxicities, lowered plasma levels lead to under-treatment. As treatment failure is common in cancer patients the implication of the herb's contribution to the failure is likely to be missed.

One of the most clinically significant interactions with tyramine rich foods like cheese, bananas, chocolate, wine etc occurs when they are concurrently used with MAO inhibitors resulting in hypertensive crises occasionally. Likewise the other significant interactions with clinical implications are seen in patients on warfarin who ingest food rich in Vitamin K such as cauliflower, broccoli, cabbage, soyabean and leafy vegetables; and those on levodopa who ingest foods rich in vitamin B_6, such as peas, pork, liver and fish, as these decrease dopamine levels resulting in antiparkinsonian effects.

Drugs, whose absorption is decreased include penicillin, tetracyclines, erythromycin, phenytoin, levodopa, digoxin.

An increase in drug absorption is seen in the case of spironolactone, griseofulvin, itraconazole.[32]

Sometimes a beneficial interaction can be seen as with ketoconazole, administered with acidic beverages, while grape fruit juice induces strong interactions when given concomitantly with diazepam, lovastatin, simvastatin, buspirone and celiprolol and to a lesser extent with antihistamines, calcium channel blockers, vincristine, arthemeter, albendazole and amiodarone.

Environment induced interactions are chiefly due to smoking that entails both pharmacokinetic and pharmacodynamic reactions. The carcinogenic polycyclic aromatic hydrocarbons in tobacco smoke are potent inducers of the CYP4501A1/1A2/and possibly 2E1 enzymes. PK interactions with smoking occur with drugs like caffeine, clozapine, olanzapine, theophylline, haloperidol and imipramine that are substrates of CYP1A2. The chief PD interactions are seen with O.C.'s, that lead to serious CVS consequences and with inhaled steroids, whose efficacy gets reduced.

Conclusions

The nature of drug interactions is complex and not an exact science due to interplay of multiple mechanisms that requires the prescriber's care in choosing or changing medication when necessary; adjusting the dose, time and sequence of administration as maybe required or continue the treatment regimen recognizing the significance of the interaction weighing the therapeutic risks versus benefits to the patient.

It is desirable to understand the basic pharmacology of drugs so as to avoid giving drugs that are additive in nature or those acting on the same or multiple sites as well as to remember the important inducers of metabolism such as rifampicin, phenytoin, barbiturates etc and the enzyme inhibitors like the azole antifungals, erythromycin, SSRI's, protease inhibitors etc.

It is prudent to remember the subsets of populations like the elderly, critically ill, and those suffering from chronic disease as they are more vulnerable to interactions due to polypharmacy or altered renal/hepatic metabolism and monitoring them carefully is to be expected as a minimal standard of care by society.

Special care is needed while prescribing certain drugs with the greatest propensity for interactions such as anticoagulants, antiepileptics, antifungals, antibiotics, antihistamines, analgesics / NSAID's, HIV protease inhibitors, proton pump blockers, anticancer drugs, hypoglycemic agents and drugs with a narrow therapeutic window.

It would be easy to conclude from the above facts that it is extremely risky to give a patient more than one drug, but this would be an over reaction, because individuals react differently, as some may be susceptible while others are not.

Finally it has to be said that it is impossible to remember or document all clinically significant drug interactions but the focus of this article was to endeavor to cover the broad mechanisms and principles of the manner in which these interactions occur exemplifying significant ones that are governed by these principles that clinicians may find useful in their practice.

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