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PHARMACOKINETICS OF DRUGS AND THEIR CONSEQUENCES FOR CLINICAL MANAGEMENT

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ABSTRACT

Drug-drug interactions are one of the most common causes of medication errors in developed countries, especially in the elderly because of poly-therapy (20-40%). Poly-therapy makes treatment more complex and thus increases the risk of clinically relevant drug-drug interactions. Drug-drug interactions can either cause adverse drug reactions or decrease clinical efficacy. DDIs can be divided into two main categories: pharmacokinetics and pharmacodynamics. In this review we searched articles published up to June 30, 2012 using the following databases: Medline; PubMed; Embase; Cochrane library; and reference lists. We discussed the mechanisms of pharmacokinetic, focusing on their clinical implications.

KEYWORDS: Absorption, Adverse drug reaction, Distribution, Drug-drug interactions, Excretion, Metabolism, Poly-therapy.

INTRODUCTION

The goal of pharmacovigilance is to figure out what the most important things are when it comes to ADRs and how they can be caused by drugs. It's also a way of measuring and

quantifying risks associated with drug use.[1] Adverse reactions are a common clinical issue and can lead to more hospitalizations and/or longer stays.[2][3]

Drug-drug interactions are one of the most common causes of adverse reactions and we found that these reactions are common in the elderly because of poly-therapy.[4,5,6,7] Poly-therapy does increase the complexity of treatment management and therefore the likelihood of clinically significant drug interactions, both of which can lead to adverse reactions.[8,9]

Direct-Diagnostic (DDI) can be divided into Pharmacokinetic, Pharmacodynamic and Additive/ Opposed (ADOPT) pharmacological effects. Pharmacokinetic effects can be broken down into three main categories: (a) Direct Effect at Receptor Function; (b) Interference with a Biological or Physiological Control Process; and (c) additive/ Opposed Pharmacological Effect. In this review, we discussed the pharmacokinetic dynamics of DDI, focused on their clinical relevance, and focused the reader's attention on pharmaceutical interactions in other original articles and review articles.

PHARMACOKINETIC DDI

Most pharmacokinetic interactions are based on understanding each drug and are determined by controlling the patient's clinical symptoms as well as changes in serum drug concentration. As mentioned above, these interactions included all the steps from absorption to excretion that we will now cover.

ABSORTION

GASTRO INTESTINAL ABSORTION

The complexity of the gastrointestinal system, as well as the actions of several drugs that interact with the digestive system, create an environment conducive to the development of DDI that could potentially affect drug bioavailability.[10] A few things can affect how well a drug is absorbed through the digestive tract. The first is the pH of the stomach. Most drugs that are taken orally require a pH of 2.5 to 3 in the stomach in order to dissolve and be absorbed.

Drugs that can increase the pH of the gastric area, such as anti-acid drugs, anti-cholinergic drugs, and proton pump inhibitor (PPI) drugs, can alter the metabolism of other concomitantly administered drugs. H2 antagonists (for example, ranitidine) and anti-acid drugs (for example, aluminium hydroxide, sodium carbamide, etc.) that increase the pH in the

gastric area will reduce thebioavailability of cephalosporin, but will increase the bioavailability of beta- blockers and tolbutamide. In addition, anti-fungal agents such as ketoconazole and antifungals require an acidic environment to be dissolved in order to be absorbed. Co-administration of these drugs with anti-fungal may result in a decrease in dissolution and absorption.[11] Therefore, you may need to take antacid, anticholinergic or PPI at least 2 hours after your anti-fungal treatment.[12] Drugs that lower gastric pH, such as enterogastrone, may have the opposite effect. The severity of drug-drug interactions (DDIs) caused by gastric pH changes is largely dependent on the pharmacodynamic properties of the drug, given the narrow therapeutic range of the drug.

Other factors that change drug absorption are complexes. For example, in this case, the digestive tract is able to combine the digestive tract with metal ions, such as calcium, magnesium and aluminium, to form poorly absorbed complexes. As a result, some drugs (such as antacids and magnesium salts-containing preparations, as well as aluminium- and calcium-containing iron-containing preparations) significantly reduce the absorption of these complexes.[13] Bile acid is a bile acid that is broken down by the body's digestive system.

Cholestyramine binds bile acids to prevent them from being broken down in the digestive system. Colestipol, on the other hand, binds to bile acids.[14] They also bind to other drugs, particularly acidic drugs (for example, warfarin or acetylsalicylic acid), sulphonamide (phenytoin), furosemide (furosemide), etc. Therefore, the time interval between the dosing of one of these drugs and another drug may be as short as possible (i.e., 4 hours).[15]

A third factor that plays a role in the absorption of DDIs is motility disorders. Drugs that increase the rate at which the drug passes through the gastrointestinal tract (for example, methocampramide or cisapride) can decrease the time at which the drug reaches the mucosa where it is absorbed, resulting in a decrease in drug absorption (for example, controlled-release drugs or drugs that are entero-protective).[16] Finally, iron can inhibit the absorption of levodopa and metildopa.

DISTRIBUTION

Drugs are typically transported by binding to plasma and tissue proteins. Among the many plasma proteins that interact with drugs, albumin, glycoprotein, or lipoproteins are the most prominent. Acidic drugs tend to bind more strongly to albumin, and basic drugs tend to bind strongly to glycoprotein or lipoprotein, or both. Passive diffusion of unbound drug to

extravascular and tissue sites is typically determined by drug concentration at active site and thus drug efficacy. Albumin is the most abundant protein in plasma. It is synthesized in liver and distributed in plasma, extracellular fluid of skin, muscle and various tissues. The intestinal fluid concentration of albumin is about 60-70% of that in plasma. Because albumin has 5 binding sites (e.g., warfarin, benzodiazepines, digoxin, bilirubin, tomoxifen) the main characterized sites are site I and II.[17]

Site I is a pocket in sub domain IIA.[18] Site II is a benzodiazepine binding site located in sub domain IIIA. Selective drug probes (ibuprofen, diazepam) for site II.[18,19]

Table No. 1: Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin.

Site 1 (Warfarin)
Phenytoin
Chlorothiazide
Naproxen
Diclofenac
Fluoroquinolones
Valproate
Sulphamidics
Site2(benzodiazepines)
Ibuprofen
Ketoprofen
Nimesulide
Dicloxacilline
Indomethacin

Free molecules interact with their target molecules and are metabolized. Other molecules enter solution to reach site of action. Plasma protein binding, as measured by the ratio of drug concentration to free drug concentration, varies significantly between drugs, and may be very high, particularly when it is >0.9. Otherwise, it is <0.2. Drugs with high levels of plasma protein binding may be preferentially displaced by drugs with higher levels of affinity for the same site. From a clinical perspective, displacement may result in symptoms, side effects, or toxicities, when the drug displaced has a higher level of plasma protein binding (>90%), a lower volume of distribution, and a narrow therapeutic index, with a faster onset of effect.

A typical example of pharmacological displacement is when warfarin is co-administered with diclofenac. Warfarin has a similar affinity to albumin, so the administration of warfarin to diclofenac to a chronically treated patient leads to the displacement of warfarin from its

binding site, resulting in an increase in free warfarin plasma concentration, resulting in serious hemorrhagic reactions.

METABOLISM

The family of enzymes known as the cytochrome P450 (CYP) enzymes plays a major role in the metabolism of many drugs. In humans, there are approximately 30 drug metabolizing enzymes belonging to families 1 to 4. However, only 6 of the 30 drug metabolism enzymes belong to the family CYP1 (CYP1A2), 2, 3 (CYP2), 3 (CYP3), 4 (CYP4), 5 (CYP5), 6 (CYP6), 7 (CYP7), 8 (CYP8), 9 (CYP9), 10 (CYP10), 11 (CYP11), 12 (CYP12), 13 (CYP13), 14 (CYP14), 15 (CYP15), 16 (CYP16), 17 (CYP17), (CYP18), (CYP19), (CYP20), (CYP21), (CYP22) and (CYP23) are primarily involved in the metabolism of drugs in the liver.[23,22,20,21]

Many drug-drug interactions (DDIs) are related to inhibition or induction of cytochrome P450 enzymes. Due to the wide variety of drugs that are metabolized by oxidative metabolism, there are a large number of clinically relevant drug interactions across multiple drug therapy regimens.

INHIBITION

Inhibition-based DDI make up the majority of clinically relevant DDI. In this process, enzyme activity is decreased due to direct interactions with a drug, typically starting with the initial dose of the inhibitor. The extinction of inhibition is associated with the drug half-life.[25,24] The metabolic inhibition can be reversible (competitious, metabolic-intermediary complex, non-competitious) or non-reversible, and the clinical effects are affected by fundamental mechanisms.

REVERSIBLE INHIBITION

1. COMPETITIVE

Competitive inhibition occurs when the inhibitor and substrate compete with each other for the same site of binding on the enzyme. This type of interaction is direct and reversible. Drugs are converted through multiple steps that are dependent on the metabolism of the enzyme that metabolizes them. These drugs are converted into nitroso- derivatives that bind with great affinity to the reduced forms of the enzymes that metabolize them. Since these enzymes are not available for further oxidation, the only way to restore their activity is by the synthesis of new enzymes, which may take several days.[26]

Omeprazole is an inhibitor of the metabolic pathway known as cytochrome P450 II (CYP2C19), which results in a decrease in antiplatelet activity. Clopidogrel is a prodrug of omeprazole that undergoes biotransformation into the active metabolite.[28] This interaction is linked to a 27% higher risk of mortality or re-incarceration in patients admitted for acute coronary syndrome.[27]

Etravirine also inhibits the activity of the metabolite cytochrome P4502 (CYP2C19). Clopidogrel Antiplatelet activity may also be inhibited by the inhibition of this metabolite. Until more data are available, the concomitant administration of a CYP 2C19 inhibitor (e.g., etravirine) and clopidogerel is not recommended.

Omeprazole therapy should be carefully evaluated in elderly patients as it may induce the development of Adverse Reactions (ADRs). In fact, we have previously reported in an elderly male that the onset of delirium was likely associated with a DDI (Direct-Initiated Diagnosis) of omeprazole via the inhibition of cYP2C19 by amitriptyline.[29]

2. NON-COMPETITIVE

In the non-competitive mode, the substrate and the inhibitor are not in competition for the active site because of the presence of an anosteric site. When a ligand binds to the anosteric site, the conformation changes in the active site, the ligand's ability to bind to the substrate decreases, and the product formation stops. Many drugs are inhibitors of non-competitive cytochrome P450 (CYP) isoenzymes, including omeprazole/lansoprazole/cimetidine.[31][30] this type of inhibition may last longer if new enzymes need to be synthesized following the discontinuation of the inhibitor drug.

IRREVERSIBLE INHIBITION

The metabolite formed when the substrate is oxidized by cytochrome P450 oxidase (CYP3A4) becomes irreversible and is covalently bonded to 3A4 resulting in permanent inhibition of this enzyme. In cases of irreversible inhibition, the critical factor is the total amount (rather than the concentration) of the inhibitor (CYP isoenzyme) that is exposed to. Lipophilic drugs and drugs with large molecular size are more susceptible to inhibition.[32] Inhibitors will reduce substrate metabolism and generally increase drug effect or drug toxicity of substrate. If it is pro drug, the effect is reduced. The co-administration of 3A4 inhibitors with the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins; e.g., simvastatin) could increase the risk of myopathy[33] and rhabdomyolysis.[34] However, it is important to

understand that during the treatment with statins it is possible the development of myopathy also for metabolic saturation, in particular during the poly-therapy.[35]

METABOLIC INDUCTION

Enzymatic drug interactions are less common than inhibition-based interactions but are just as deep and clinically relevant. Environmental pollutants and a large number lipophilic drug class can cause the induction of these enzymes. The mechanism of action is often transcriptional activation, resulting in an increase in the synthesis of more cytochrome P450 (CYP) enzymes.[37] Induction simply increases the amount of circulating P450s and accelerates the oxidative and clearance of the drug.[36] The most commons enzyme inducers are rifampicin phenobarbital, phenytoin, carbamazepine, and anti-tubercular drugs.[38]

Rifampicin stimulates the liver to produce enzymes known as cytochrome P450 IIA (CYP2A2A2A6, CYP2C and CYP2B6). However, there is little evidence of induction of other types of CYP enzymes. A large number of drugs are excreted by rifampicin. However, most of these drugs are substrates of the metabolite (CYP3A4) metabolite (midazolam), such as quinidine, ciclosporin, cyclosporin A and many steroids. Rifampicin has a very short half-life (24 hours), so the induction of enzymes like CYP3A4 and CYP2C becomes apparent within 24 hours. Phenobarbital has a very long half-life (3-5 days), so it takes about 1 week for induction of enzymes like CYP3A4 and CYP1A2 and CYP2C to become apparent. These enzyme induction reactions also happen with smoking and with long-term consumption of alcohol or drugs, and can increase the time it takes for a drug to work by increasing the metabolic elimination of the drug.

EXCRETION

The organs and vehicles responsible for drug elimination are the kidneys, the liver, the lungs, feces, perspiration, saliva, and milk. Drug excretion via saliva, perspiration, and lungs (in the case of volatile drugs) is of little quantitative importance, but milk is important when drugs can reach the infant during lactation. Drug excretion occurs primarily through renal tubular excretion, renal filtration (glomerular reabsorption, active tubular secretion), and biliary excretion.[38] The drugs that are eliminated from the body can have many interactions. For example, one drug in this organ is eliminated by another drug in the same organ from which it is eliminated.[39]

The kidney is the body's primary route of elimination for drugs and drug metabolites. Drug-drug interactions may occur for competitive reasons at the active tubular (tubular) secretion level, where 2 or more drugs utilize the same transport mechanism. For example, NSAIDs (nonsteroidal anti-inflammatory drugs) cause toxic effects by blocking the kidney's excretion of their active metabolite (methotrexate).[40] It was also demonstrated that amoxicillin decreased the renal clearance of methotrexate.[41] Probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, increases of 2.5 times the area under the AUC of oseltamivir.[42]

Tubular transport is affected by several drugs. Cimetidine, one of the H2 receptor inhibitors, is one of the drugs that may affect tubular secretion. Cimetidine has been shown to affect the tubule secretion of various molecules. The effect of cimetidine on the flux and efflux of organocatalytic cations through HOPT (Human Organic Cation Transporter ([HOPT1 and hOPT2] and Human Multidrug and Toxin Extrusion (HMT)) could alter other drug serum concentrations despite normal renal function.[44]

In particular, when the urinary pH is alkaline, acid drugs are less likely to be absorbed, and when the pH is acidic, basic drugs are not as likely to be absorbed. However, the changes in urine pH are only relevant when the pKa (i.e., the point where 50% of molecules in solution are ionized) of the drug is in the range of 7.5 to 10.5 (for the bases) and 3.0 to 7.5 (for acids). These pKa values have the potential to significantly change the degree of drug dissociation. Compounds like ammonium chloride (chloroform) and tromethamine (dihydrocannabinol) are able to change urinary pH, and this may affect the elimination of several acid and basic drugs.[12] On the other hand, the interaction of diuretics with lithium salts may still have adverse consequences on the patient.

Acidic and basic drugs with high ionization levels are transported by active transport through epithelium in the renal tubule. The rate of transport of molecules is dependent on the availability of a transporter, which is a protein that facilitates the transfer of molecules through the cell membranes. When two drugs are substrates of the same transmembrane, Transporter, they can complement each other until the transmembrane capacity is reached. At that point, the elimination rate approaches zero order (saturation).

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availability of a transporter, which is a protein that facilitates the transfer of molecules through the cell membranes. When two drugs are substrates of the same trans membrane transporter, they can complement each other until the transmembrane capacity is reached. At that point, the elimination rate approaches zero order (saturation).

STRATEGY TO PREVENT PHARMACOKINETIC DDI

If you're a health care professional, the SPCs are the main source of information about DDI. Unfortunately, it's hard to list all the DDI risks, so the SPCs may not be able to give you all the info you need. For example, an Italian study looked at the risk of DDI with PPI users and found that 3.0% were exposed to it within 1 year, according to the SPCs. But when you looked at the information on DDI risk with PPI from Drugdex, it was three times higher at 9.0%. Even if it's not always possible and affordable, setting up therapeutic drug monitoring protocols for the patients mentioned above (e.g., elderly people with co-morbid conditions treated with multiple medications) should be seen as an important tool to reduce the number and severity of drug-related overdoses that could lead to either an increase in healthcare costs for the Health System or a liability for the clinicians.

We're hoping the National Health System will come up with a plan to keep doctors up to date on DDI, especially with drugs that are used a lot. But right now, it's best to look at reports on DDI that look at different sources, updated with the latest info from the research. That way, we can figure out if there's a risk of DDI, especially for older people who use poly-therapy. Genetic polymorphism in certain types of cytochromes P450 enzymes has been linked to drug treatment and drug-drug interactions (DDIs) in the past.[7] So, even though it might not always be possible and affordable, both therapeutic drug monitoring for patients with multiple drug therapy and predicting the role of polymorphism in CYP enzymes in DDIs should be seen as a tool to reduce the number and severity of DDIs.

CONCLUSION

Drug-drug-impaired (DDI) is a common issue when treating patients with multiple drugs. But it's important to remember that there are only two drugs that can trigger a DDI, even if the clinical relevance of each drug is related to its own pharmacology. A DDI will only work when there are drugs with a lower therapeutic index, longer half-life, and a higher binding to plasma proteins. It's also important to remember that DDI isn't a problem with a class of drugs, but with a single drug, and this issue could be underestimated if we only look at the SPC.

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