Original Research Paper

Volume - 10 | Issue - 6 | June - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Clinical Science

COMMON CARDIOVASCULAR MEDICATION INTERACTIONS

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ABSTRACT There are various classes of cardiovascular drugs and other drugs used in the cardiac patient to treat comorbid conditions.To reduce the mortality and morbidity in cardiac patients and for the treatment of comorbidites ,the prescription contains multiple drugs leading to polypharmacy. Medication errors are mainly caused due to drug interactions. With the increase in number of comorbidities,there is increase in number of drugs in prescription, With increase in the number of drugs prescribed,potential drug-drug interactions increases.Based on pharmacokinetics and pharmacodynamics of the drug,with slight modification in the dosage regimen most of the DDIs can be avoided.To reduce the risk associated with DDIs improved awareness among prescribers is required. While prescribing,use of drug groups commonly involved in potential DDIs should be minimized and optimized.Here we summarise the drug-drug interactions,mechanisms and clinical management of common cardiac medications.

KEYWORDS : Drug-Drug interaction,factors,mechanism,clinical management.

INTRODUCTION:

A drug –drug interaction[DDI] is defined as the modification of the effect(s) of one drug by the the another drug which is administered prior (or)concomitantly.The response of a drug is modified due to DDI[7]. Changes in either drug efficacy or drug toxicity for 1 or both of the interacting medications may be resulted by DDI[5]. Drug interactions are pharmacodynamic or pharmacokineticin nature. A pharmacodynamic drug interaction and pharmacokinetic drug interaction is related tothe drug's effect on the body and body's effect on the drug respectively. Examples of pharmacodynamic and pharmacokinetic DI are sedation caused due to combination of alcohol with other medications and Renal insufficiency causing increase in the systemic concentration of a renally eliminated drug respectively. Synergism, antagonism, alteration of effect or an immune mediated idiosyncracy results from a pharmacodynamic DI[7].An alteration in absorption, distribution,metabolism, or elimination of a drug causes a pharmacokinetic DI[9].The occurrence of drug interaction increases as the number of concomitant medications increases. The drug-drug interaction severity and likelyhood varies and depends on the pharmacokinetic and pharmacodynamic properties of the object drug and the precipitant drug.Because of the types and number of drugs cardiovascular patients receive,they are at high risk for drug drug interactions[3]. The risk of DDI when two to four drugs are used is estimated at approximately 6% , 50% with five drugs and nearly 100% with eight drug[9].

Classification of drug-drug interactions includes,a)contraindicated drug interaction,in which drugs are contraindicated when used concurrently,b)Major drug interaction,it may be life threatening interaction ,to minimize or prevent serious adverse events, medical intervention is required, c)Moderate drug interaction which leads to exacerbation of patient's condition and or alteration in the therapy is required,d)Minor drug interaction,limited clinical effects like increase in frequency or severity of side effects are included in interaction, but generally major alteration in the therapy is not required[12]

FACTORS CAUSING DRUG-DRUG INTERACTIONS[DDIs]:

The drug– drug interactions risk is increased by polypharmacy, advanced age, medications requiring intensive monitoring or medications with a narrow therapeutic index..In the heart transplant recipient all of these factors are present except advanced age[4].The concomitant use of more than two medication is called polypharmacy.As elderly patients usually have comorbid illnesses,polypharmacy practice is common in them. The DDIs in elderly are caused due to polypharmacy and complicated drug regimens used for treating the comorbidities.As per the studies,one of the major risk factors in precipitation of DDIs is polypharmacy. Because of decreased functioning of the systems, more number of medications due to comorbidities and multiple drug regimes,the elderly population are at increased risk for DDIs[12]. Patient-related and drug-related factors results in a 10-fold interpatient variability in the magnitude of a drug interaction . Age,sex,lifestlyle,genetic polymorphisms causing differences in enzyme expression or activity, and disease impairment affecting drug metabolism[5],concomitant diseases, genetics, diet, and environmental exposures are the patient-related factors predisposing to drug interactions.Commonly used immunosuppressants, antifungal agents, and lipid-lowering medications which are metabolized through the cytochrome P450 (CYP450) enzyme system and effluxed from cells by the multiple drug resistance transporter protein p-glycoprotein (P-gp) are some of the examples.Genetic polymorphism is exhibited by both systems and are found in the liver and gastrointestinal tract.Superfamily of oxygenases includes CYP450 enzymes; Oxygenases primary purpose is to add a functional group to a drug to increase its polarity and to promote its excretion from the body.Enzymes are grouped together into families designated by an Arabic numeral (eg, the CYP1 family) if enzymes possess >40% homology.A letter after the number (eg, CYP2C and CYP2D subfamilies) is a designation for subfamilies which are divided after families,Each subfamily members have >55% homology with each another.To identify a specific enzyme pathway individual members are given an additional number (eg, CYP3A4).60% of oxidized drugs, including the calcineurin inhibitors (CIs) cyclosporine (CSA) and tacrolimus (TAC),sirolimus (SIR), and everolimus (EVER), undergo biotransformationthrough CYP3A4 enzyme system,so it is particularly important.The superfamily of ATP-binding cassette transporters includes a membrane bound glycoprotein called P-gp.P-gp acts in a protective capacity by “effluxing” drug from the cell membrane or cytoplasm like the CYP450 enzyme system. Within the small intestine, proximal tubules of the kidney, and biliary canalicular membranes P-gp density is highest.Both the CYP450 enzyme system and P-gp are used by some medications such as CIs and SIR, making them especially susceptible to drug interactions.Inhibitors and inducers of the CYP450 enzyme system,P-gp and substrates are reviewed extensively[4].

Drug-related factors include the individual pharmacokinetic characteristics of each medication implicated in the DDI (eg, binding affinity,half-life [t1/2]), dose of the medications, serum concentrations, timing and sequence of administration, and duration of therapy[5].Several intricate elements are involved with the absorption of a drug after oral administration,all of which can be possible targets for drug– drug interactions: intestinal luminal absorption (drug dissolution, lipophilicity, and stability), intestinal delivery (gastric pH, gastric emptying and presence of food),active intestinal drug efflux

pumps and metabolism (P-gp, CYP450 enzyme system), and hepatic first-pass metabolism (phase I and II metabolism).The area under the curve (AUC), which reflects medication bioavailability, and mean maximum blood concentrations for the dosing interval (Cmax) are pharmacokinetic parameters commonly used to evaluate drug interactions.When a drug potentiates or diminishes the effect of another a pharmacodynamic interaction occurs[5].

TABLE- Mechanism of action of drugs interacting and their management

DRUGS USED IN CARDIAC TREATMENT	DRUG INTERACTING	CLINICAL CONSEQUENCE	MANAGEMENT
ANTI HYPERTENSIVES BETA BLOCKERS[3]			
β-blockers	Diltiazem, verapamil,digoxin	Bradycardia or heart block	Monitor HR,PR adjust dosage if needed
β-blockers	Disopyramide	Negative inotropic effect	Monitor HR signs snd symptom of reduced cardiac output
B-blockers	Clonidine	Rebound hypertension following withdrawl of clonidine	Use atenolol or metaprolo .withdraw β-blocker initially then withdraw clonidine them monitor BP
B-blockers	Prazosin,terazosin, doxazosin	Augmentation of first dose syncope	When α-blocker is given to patient with β-blockerstart with low dose monitor bed time dosing of α-blocker
β-blockers	Theophylline B-agonists	Increased bronchodilatory effects and more with non selective β-blockers	Use cardioselective β-blocker
β-blockers	NSAIDS	Reduced β-blocker effect upon longterm use of NSAID	Monitor BP and angina frequency,adjust dose of βblocker ,use NSAIDS only for short period.
β-blockers	Dipyridamole(IV)	Bradycardia &asystole	Discontinue β-blocker prior to dipyridamole
Atenolol	Ampicillin	Reduced atenolol effect	Monitor HR&BP,increase atenolol dose if needed
	Risperidone	Atrial fibrillation	-
Propranolol	Chlorpromazine Thioridazine Thiothixene	Neuroleptic toxity, chlorpromazine may increase the effect of propranolol	
DIURETICS[10]			
Diuretics	Digoxin	Hypokalemia	Monitor potassium levels
Diuretics	Aspirinand thiazide diuretics	Hyperurecemia	Monitor uric acid levels
Diuretics	NSAIDS(2)	Decreased loop diuretic activity	Monitor,BP and use acetaminophen instead of NSAIDS
Diuretics	Steroids	Hypokalemia and sodium retention	Supplement potassium monitor potassium levels
Diuretics	Aminoglycosides and antibiotics	Ototoxiticity[loop diuretics]	Avoid the combination
ACEIs &ARBs[10]			
ACEIs&ARBs	Potassium sparing diuretics	Increased potassium levels	Monitor BP
ACEIs &ARBS	NSAIDS	Sodium and fluid retention	Avoid comination
ACEIs&ARBS	High dose aspirin	Decresed anti hypertensive activity	Avoid the combination
CLONIDINE	Centrally acting depressants [hypnotics,tranquillizers,neuroleptics,anti-epileptics,anti deprassants,alcohol]	Increased sedation effect	Instruct patient to take night time and avoid driving and using machinery
HYPOGLYCEMIC AGENTS[12]			
Insulin	Metaprolol	Masks symptoms of hypoglycemia	Monitor Blood glucose levels/HBA1C
Insulin	Telmisartan,ramipril,metformin ,losartan	Increased risk of hypoglycemia	-
Insulin	Levofloxacin	Impaired glycemic control	-
Metformin	Ramipril	Increased risk of hypoglycemia	-
Thiazolidinediones	CCBS,NSAIDS	heart failure	Avoid combination.
LIPID LOWERING AGENTS[5,8]			
Statins	Cochicine	Increasedrisk for muscle toxicity	Combination may be considered.monitor muscle toxicity
Statins	Fenofibrate	Increased muscle toxicity	Combination is reasonable
statins	Gemfibrozil	Decreased statin activity and increased muscle toxicity	Combination should be avoided with lovastatin, pravastatin, simvastatin.
Atorvastatin	Verpamil, clarithromycin, itraconazole, fluconazole, cyclosporine	rhabdomyolysis	Avoid combination better use rosuvastatin
Atorvasatin	Clopidogrel[12]	Decreased antiplatlet activity	-
Atorvastatin	Risperidone[1]	Myalgia	Inhibition of CYP3A4 by risperidone an increase in concentration and side effects of atorvastatin

lovastatin ,simvastatin[5]	Ticagrelor	Decreased metabolism of statin and increased rik of muscle toxicity,incresed statin exposurewhen given with atorvastatin	Combination is considered,limit dose to 40mg
Fluvastatin,lovastatin,rosuvastatin ,simvastatin	Warfarin	Increased INR and high risk of bleeding	Combination is useful
Statin+ immunosuppressants	Cyclosporine/ tacrolimus/ sirolimus/ everolimus	Increased statin concentratration and muscle toxicity	Should be avoided with lovastatin and simvastatin. combination is considered with other drugs by limiting dose
Cholestyramine	Mycophenolate mofetil	Decreased MPA exposure	Avoid concomitant use[5]
IMMUNOSUPPRESSANTS[4]			
Cyclosporine/tacrolimus	Ticlopidine	Decreased CSA/TAC exposure	Monitor TAC/CSA levels for several months
CSA/TAC	Clopidogrel	decreased action of clopidogrel	Monitor for increased clotting
CSA/TAC	Amiodarone	IncreasedCSA/TAC activity	Check CSA/TAC levels every 3days for 1st week,weekly for 1st month,then periodically use low dose of immunosuppressants
CSA/TAC	Chloramphenicol[11]	Increased CSA/TAC concentration	MonitorCSA/TAC concentration and renal function.adjust dose appropriately
Azathioprine[4]	Allopurinol	Anemia,leukopenia,TCp	Decrease AZA dose by75-80%
	Warfarin	Decrease INR/PT	INR /PT should be monitored atleast 2times weekly
Sirolimus	Diltiazem	Increased sirolimus activity	Monitor sirolimus levels 3 times/OW for 1st week
ANTIPLATLET AGENTS[12]			
Aspirin	Clopidogrel	Increase risk of bleeding	-
	Furosemide	Decreased diuretic activity	-
	Metaprolol	Decreased metaprolol activity	-
	Insulin	Hyper/hypoglycemia	-
	Ramipril, enalapril	Decreased anti hypertensive activity	-
	Cilostazol	Increased risk of bleeding	-
Clopidogrel	Amlodipine	Decreased antiplatlet activity	
	Warfarin[10]	Increased INR/bleeding	Monitor for bleeding
	Paclitaxel[13]	CYP3A4 inhibition	Monitor for neuropathy and nephropathy
CARDIAC GLYCOSIDE[6]			
Digoxin	Cholestyramine	Effects Adsorption of digoxin	Administer digoxin 8hours before cholestyramine, use solution or capsule form of digoxin
Digoxin	Antacids	-	Maintain TOA
Digoxin	Kaolin –pectate	effects Adsorption of digoxin	Use solution or capsule form of digoxin and give digoxin 2hours before kaolin pectate
Digoxin	Neomycin, paraaminosalicyclic acid,sulfasalazine	-	Increase dose of digoxin
	Spiranolactone	Decreased clearance	Measure serum digoxin
Digoxin	Erythromycin, tetracycline	Increased bioavailaabity of digoxin by increased metabolism	Measure sr.digoxin,decrease digoxin dose,use solution/capsule
Digoxin	Quinidine	Decreased bioaailabilty, vd and clearance	Decrease dose by 50% and measure serum digoxin concentration
Digoxin	Amiodarone, verapamil	Decreased renal and non renal clearance	Decrease dose by 50% and measure serum digoxin concentration
Digoxin	Tiapamil	-	
Digoxin	Triamterene	Decreased non renal clearance	Measure serum digoxin
Digoxin	Indomethacin	Decreased renal clearance	Decrease dose by 25%
Digoxin	Tetracycline[11]	Increased digoxin concentration	Monitor and adjust dose
ANTIARRYTHMICS			
Procainamide[11]	Trimethoprim-sulfamethoxazole	Increase in procainamide concentration	Monitor and adjust proacainamide dose
Amiodarone	Rifampin[11]	Increase in amiodarone metabolism	Avoid concomitant use
	Aripiprazole[1]	Akathisia,tremors, extrapyramidal disorder	Inhibition of aripiprazole metabolism by inhibiting CYP2D6
	Clozapine	Sialorrhea,akathisia	Escalation of drug concentration-inhibitionof CYP2D6
Felcainide	Olanzapine	Pancreatitis	Inhibition of olanzapine metabolism by CYP2D6 activity
Mexiletine, tocanide	Rifampin[11]	Increased clearence	Monitor dysarrythmia and adjust dose

Propafenone	Olanzapine[1]	Gynecomastia galactorrhoea	Inhibition of olanzapine metabolism of CYP1A2,CYP2D6
Quinidine	Rifampin[11]	-	Avoid its usage/monitor concentration

WARFARIN[11]

When used concomitantly with warfarin ,drugs with moderate to high risk of increased INR and/or bleeding tendency

DRUG	CLINICAL MANAGEMENT	DRUG	CLINICAL MANAGEMENT
Metranidazole	When starting or stopping monitor INR, when adding metronidazole decrease dose of warfarin by 30%	Levothyroxine	When starting or stopping monitor INR
Amiodarone	when starting or stopping monitor INR, when adding amiodarone decrease dose of warfarin by 25%	Ciprofloxacin, levofloxacin	When starting or stopping monitor INR, when adding ciprofloxacin decrease dose of warfarin by 15%
Aspirin(6gms/day), NSAIDS	monitor for bleeding,Use lower doses of aspirin,use COX-2 inhibitors	Phenytoin	Initially increased INR is seen,it is decreased later on with long term use – monitor INR, alternative antiepileptic drug should be used
Imatinib [14]	Refer low molecular weight heparin or standard heparin instead of warfarin.	Fluconazole, itraconazole	When starting or stopping monitor INR, when adding fluconazole &itraconazole ,decrease dose of warfarin by 20% &25% respectively.
Ranitidine	when starting or stopping monitor INR,use alternative (famotidine)	Tramadol	When starting or stopping,monitor INR, when adding tramadol decrease dose of warfarin by 20%
Sulfamethoxazole	Interaction is severe, Monitor INR, when adding sulfamethoxazole decrease dose of warfarin by 25%	Isoniazid , Rifampicin	When starting or stopping, monitor INR, when adding isoniazid & rifampicin decrease dose of warfarin by 15% & 20-25% respectively.
Clarithromycin	when starting or stopping monitor INR, when adding clarithromycin decrease dose of warfarin by 15%	Chloramphenicol[11]	Monitor INR.

,**CSA/TAC-**cyclosorine,tacrolimus,**COX-**cyclooxygenase,**CYP-**cytochrome enzymes,**OW-**once weekly,**PT-** prothrombin time,**NSAID-** non steroidal anti inflammatory drugs.

CONCLUSION:

Patients with cardiovascular disease also have co-morbidities and are at high risk for DDIs. As informed earlierpolypharmacy is one of the main cause for drug-drug interaction. Number of DDIs increase with increase in number of drugs prescribed. Health care providers should be knowledgeable about dose limits, monitoring parameters to minimize the toxicity. Clinical decision should be associated with the search for optimal ,as safe as possible,drug combinations.

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