COMMON DRUG INTERACTIONS IN CARDIOLOGY PRESCRIPTION

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INTRODUCTION

Drugs predominantly act through cellular pathways and there is every chance of interaction with each other if both drugs share same pathways for either their action or metabolism. Both the cases will interfere the bioavailability and action of the one or both the drugs.

It is essential to determine the pharmacokinetics and pharmacodynamics of various cardiac drugs in order to minimize the interaction of prescribed drugs. A good knowledge of cardiac drug interaction will help physician to take decision during critical care to stop a certain drug over another to get desired result, at the same time polymorphism in patient's gene should also be accounted for such variability in drug action.

DRUGS COMMONLY USED IN CARDIOLOGY PRACTICE:

There are certain drugs which are predominantly used in cardiac medicine are:

1. Antihypertensive: ARB *(*angiotensin receptor blocker), CCB (calcium channel blocker), ACEi (angiotensin-converting enzyme inhibitors), diuretics.
2. Anti-dyslipidemia: Statin, nicotinic acid.
3. Anti-platelet drug: Aspirin, GP IIb/IIIa antagonist.
4. Anti-coagulants: coumadins, heparin.
5. Anti-arrhythmic: amiodarone.
6. Anti-Heart failure: Beta blocker, ACEi.

Causes of Common Drug Interaction:

1. Pharmacodynamic (what drug does to your body)
2. Pharmacokinetics (what body does to drug)
3. Effect of genetic polymorphism for variable pharmacokinetics of drug.

Common pharmacodynamic drug interaction:

1. Concurrent use of anticoagulant and antiplatelet drug is a classic example of pharmacodynamic drug interaction. Using heparin or warfarin with aspirin or clopidogrel mutually enhance (OR, 1.53; 95% CI, 1.05 to 2.22) the bleeding complication (Shireman et al. 2004).
2. Non-hydropyridine CCB (Verapamil) when concomitantly used with beta-blocker (Carvedilol) may induce bradycardia.
3. Concomitant use of Sildenafil with nitrate (vasodilator) may result in severe hypotension even sudden cardiac death.
4. Co administration of ACEi with potassium-sparing diuretics causes hyperkalemia, more so in diabetic patients.

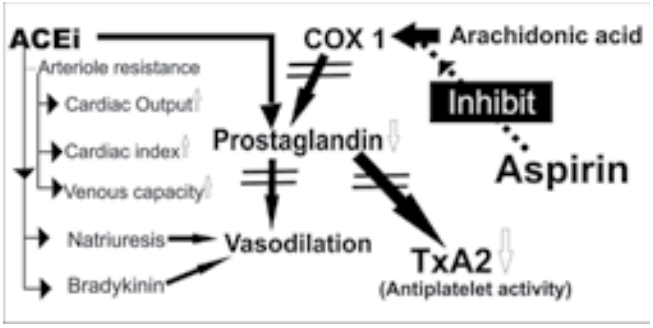

Fig. 1: Interaction of ACE inhibitor (ACEi) and Aspirin which results in possible loss of function of ACEi. Cox1: cyclo-oxygenase 1, TxA2: Thromboxane A2.

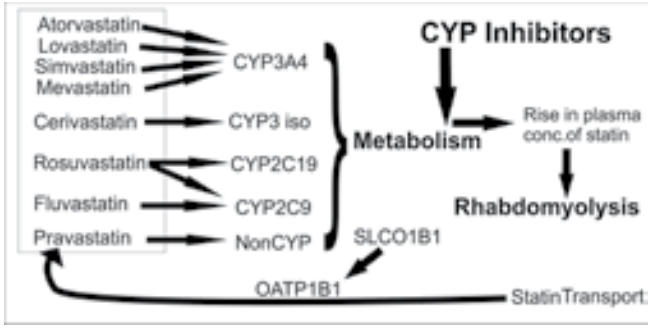

Fig 2: Possible route of statin metabolism and adverse effect. CYP= Cytochrome P450.

DRUG INTERACTION BETWEEN ANTIHYPERTENSIVE AND ANTIPLATELET AGGREGATOR:

Aspirin with ACE inhibitor (ACEi):

Aspirin is frequently prescribed with ACE inhibitor. Prostaglandin activity is the point of confliction between these two drugs where aspirin severely inhibit the activity of prostaglandin while ACE inhibitor needs the activity of prostaglandin for its optimal response (Fig 1).

Effect of inhibition of prostaglandin is not so pronounced in normotensive and euvolemic subjects. In hypertensive subjects, inhibition of prostaglandin hampers the effect of nearly every antihypertensive drug including ACE inhibitor. As ACE inhibitor is immensely effective in controlling remodeling of heart and thus reduce the heart failure, concurrent use of aspirin and ACE inhibitor in moderate to high degree of heart failure patient will reduce the effect of ACE inhibitor (Hall et al.2000), though it was countered by Latini et al. 2000.

Reports from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) (Nguyen et al. 1997) and Studies of Left Ventricular Dysfunction (SOLVD) (Rand et al. 1998) suggested the attenuation of ACE inhibitor response when aspirin was used concomitantly.

Peterson & Laurer (2011) recommended the low dose and non-long term aspirin therapy in concomitant with ACEi or using alternate anti-platelet therapy like clopidogrel (if patient is nonresponsive to low dose aspirin with ischemic event) and restriction in use of NSAID with ACEi for the same reason.

REDUCED ACTIVITY OF ASPIRIN IN CONCOMITANT USE WITH OTHER NSAID

Use of Non-steroidal anti-inflammatory such as ibuprofen will eliminate the protective effect of aspirin and physician should be careful to determine which analgesic best suitable in patient with heart failure.

The possible cause of this interaction

Arachidonic acid binds to COX-1 (Cyclooxygenase-1) and converted to TXA_2 (Thromboxane A_2) to stimulate the platelet for aggregation. Aspirin blocks the access of arachidonic acid and inhibits the production of TXA_2 and thus prevent the platelet aggregation. If ibuprofen (NSAID) is administered concurrently with aspirin, Prior reversible occupancy of ibuprofen inhibits aspirin from permanently binding to COX-1. However, aspirin differs by irreversibly acetylating a serine residue at position 530 within the channel, blocking access of arachidonic acid to its catalytic site, while other NSAIDs are reversible inhibitors of the catalytic site. The mechanism proposed is that ibuprofen inhibits the access of aspirin to the COX-1 acetylation site in platelets resulting in antagonizing irreversible platelet inhibition.

REDUCED BIOACTIVITY OF STATIN DUE TO DRUG INTERACTION AND GENE MUTATION IN ITS TRANSPORT SYSTEM:

Statin is common cholesterol lowering drug by affecting the HMG-Co-A reductase enzyme responsible for cholesterol formation.

Possible causes of diminished statin activity:

1. Statins are transported to Liver via an enzyme OATP1B1 (organic anion-transporter B1) which is encoded by SLCO1B1 (Solute carrier organic anion transporter family, member 1B1) gene. If statins are not successfully metabolized, their level in blood will be increased which may result in rhabdomyolysis or myopathy. Common SNP (single nucleotide polymorphism) in SLCO1B1 gene (SLCO1B1*5, c.521T>C, protein p.V174A, rs4149056) can cause impairment of statin transportation to Liver leads to high level of statin in circulation (Niemi et al.2011).
2. Statins are predominantly metabolized through CYP (Cytochrome P) isozymes in the Liver. Most of the statins (Simvastatin, Atorvastatin, Lovastatin, Mevastatin)are metabolized through CYP3A4.Some statin including rosuvastatin and Fluvastatin use CYP2C19

Table 1: Different CYP3A4 inhibitor drug stratified according to their potency.

High	Antibiotics	Clarithromycin, Telithromyocin, Chloramphenicol
	Antifungal	Azole
	Antidepressant	Nefazodone
Moderate	CCB	Verapamil, diltiazem
	Antibiotics	Erythromycin
	Herbal therapy	Grape fruit juice
Unspecified potency	Amiodarone	
	Ciprofloxacin	
	Norfloxacin	
	Dithiocarbamate	

Table 2: Profile of Reports of Rhabdomyolysis Associated With selected statins (modified after Omar et al. 2002)

Statin	Frequency of Reports/Unique Cases	No. of Cases Associated With Potentially Interacting Drugs* (n)	
Simvastatin	321/215	Fusidic acid (1)	Azole antifungals (4)
		Fibrates (33)	Chlorzoxazone (2)
		Cyclosporine (31)	Nefazodone (2)
		Warfarin (12)	Niacin (2)
		Macrolide antibiotics (10)	Tacrolimus (1)
		Digoxin (9)	
Cerivastatin	231/192	Fibrates (22)	
		Digoxin (7)	
		Warfarin (6)	
		Macrolide antibiotics (2)	
		Cyclosporine (1)	
Lovastatin	51/40	Cyclosporine (12)	Digoxin (2)
		Macrolide antibiotics (11)	Nefazodone (2)
		Azole antifungals (6)	Niacin (1)
		Fibrates (5)	Warfarin (1)

& CYP2C9 for their metabolism, though pravastatin is metabolized through non-CYP pathway (Fig 2). Concomitant therapy of CYP3A4 inhibitor (Table 1) with simvastatin results in rhabdomyolysis (Rowan et al., 2010).Though no such data is available for other statins using same CYP3A4 pathway (Atorvastatin, Lovastatin, Mevastatin), but similar result should be assumed for them for such concomitant therapy (Table 2).

Possible alternate regime:

1. Genetic test rarely required to rule out statin toxicity.

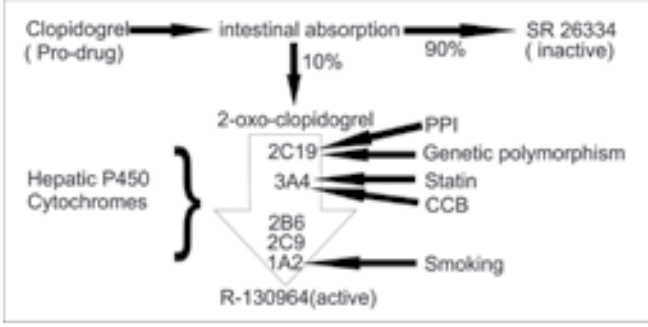

Fig. 3 : Variable pharmacodynamic responses of Clopidogrel under different interactions (modified after Tantry et al. JACC, 2011).

2. If CYP3A4 inhibitor is necessary, then either statin therapy should be stopped or use rosuvastatin or pravastatin. (Simvastatin & atorvastatin to be avoided).

DRUG INTERACTION OF CLOPIDOGREL:

Fig 3 demonstrates that only 10% of total infused Clopidogrel is absorbed in system and then uses several P450 group of enzymes, i.e. 2C19, 1A2, 2B6, 3A4 to be metabolized into active form.

Several chemical hypotheses are there which predict the worsening of pharmacokinetic response of Clopidogrel:

1. Polymorphism in 2C19 enzyme may result into poor metabolism of Clopidogrel which is accepted in epidemiological study. A SNP CYP2C19(*)2 (or 681 G > A) can cause an increased risk of major adverse cardiovascular events in the follow-up (RR: 1.96 (1.14-3.37); P = 0.02). When studies evaluating stent thrombosis (n = 4) for a total of 4975 patients were considered, the presence of the variant allele was associated with an increased risk of stent thrombosis (RR: 3.82 (2.23-6.54); P = 0.0001). (Sofi et al. 2011).
2. Statin and CCB has competitive utilization of CYP3A4 enzyme with Clopidogrel for metabolism which may reduce the activity of both the drugs (Clarke et al, 2003, Jolanta et al. 2008). But epidemiological study shows that there is no competitive interaction of statin and clopidogrel (Saw et al. 2007, Mukherjee et al. 2005, Schmidt et al, 2011).
3. Most striking interaction is happened between smoking and activity of clopidogrel. Smoking induces the activity of CYP1A2 and thus enhances the metabolism and in turn efficacy of clopidogrel. Some epidemiological studies corroborate this hypothesis (Jae Kean Ryu, 2010; Berger et al. 2009) which is contradicted by recent study (Sibbald et al 2010).
4. An interaction between PPI (proton pump inhibitor) and clopidogrel is possible when the both agents are taken with Grapefruit juice. PPI use CYP 3A4 while Clopi-

Table 3: Important Amiodarone Drug Interactions

Drug	Result of interaction
Digoxin	Elevated digoxin plasma concentration
Warfarin	Elevated prothrombin time
Simvastatin	Increased incidence of myopathy when simvastatin dosage is higher than 20 mg per day
Sildenafil	Increased sildenafil plasma concentration
Cyclosporine	Increased cyclosporine plasma concentration
Antiarrhythmic drugs	Additive effects: possible elevated plasma concentrations of quinidine, disopyramide, flecainide, propafenone and dofetilide.
Quinolones	Additive QT effect: possible increased risk of proarrhythmia
Antidepressants	Increased plasma concentration of drugs metabolized in liver: possible increased risk of proarrhythmia

dogrel use CYP 2C19 which has no impact to each other. As grapefruit juice use the CYP3A4 which shunted the PPI metabolism through 2C19 may diminish the clopidogrel response.

5. St John's wort is a potent inducer of both CY3A4 and 2C19 pathways and simultaneous administration this with clopidogrel and any of the PPIs may lead to significant drug interactions.

Possible alternate regime:

1. Grapefruit juice or St John's wort should not be taken with PPI and Clopidogrel medication.
2. Though trial data is still to draw any conclusion about interaction between statin and clopidogrel, care should be taken in high risk patients. Either nonCYP statin (Pravastatin) should be used or statin should be used in low dose to avert the interaction with clopidogrel, else alternate antiplatelet therapy (prasugrel) should be introduced if statin is essential for patient.
3. In case of concomitant use of CCB and clopidogrel, response of both the agents should be closely monitored to avoid any interaction.

INTERACTION OF AMIODARONE WITH OTHER DRUGS:

Amiodarone is widely used anti-arrhythmic drug particularly in life threatening ventricular arrhythmia.

Pharmacokinetics:

1. Possess very high content of iodine which may be a cause of its interaction with thyroid gland.
2. Bioavailability is generally poor (22-94%) and well absorbed when taking with food
3. Amiodarone is lipid soluble and stored in fat and muscle in a high concentration. As amiodarone crosses the placenta and secreted in breast milk also.
4. Desethylamiodarone (DEA) is active metabolite of amiodarone to have anti-arrhythmic property.
5. Due its slow release from lipid rich tissue its half-life is generally high (mean 58 days).

DRUG INTERACTION OF BETA BLOCKER:

B-adrenergic receptor blocker has both pharmacokinetic and pharmacodynamic interaction with other drugs.

Pharmacodynamic interaction*:*

1. Non-hydropyridine CCB (Verapamil or diltiazem) when concomitantly used with beta-blocker may induce sinus bradycardia and AV block of various types. But such combination is useful in patients with AF and FVR, particularly in patient with MS and FVR and symptomatic CV dysfunction.

Pharmacokinetic interaction*:*

1. Beta blockers (specially propranolol and metoprolol) are generally metabolized in Liver and have high first pass clearance. Many enzyme inducing drugs increase the clearance of metabolized beta blocker and in turn reduce their bio-availability.
2. Cimetidine is reported to have role in clearance of propranolol and metoprolol by enhancing the peak plasma level by 70% & 95% in concomitant therapy with cimetidine (Kirch et al. 1981).
3. First pass clearance is also dependent on hepatic flow. Hydralazine in this way reduces the first pass clearance of propranolol and metoprolol which increases the plasma concentration of the beta blocker.

Cardiac drug interaction with alternate medicine or herb:

1. Findings suggest that Ginkgo biloba extract reduces the therapeutic potency of the Calcium channel blocker, nicardipine (Shinozuka et al. 2002).
2. Ginger reinforces warfarin action by heterogeneous mechanisms. It should thus not be used in patients on oral anticoagulant and/or antiplatelet therapy (Argento et al.2000).
3. Clove may increase the risk of bleeding or potentiate the effects of warfarin therapy (Heck et al. 2000).
4. Garlic with warfarin or aspirin causes bleeding complication (Vaes and Chyka, 2000).
5. Guggul is an ayurvedic anti-dyslipidemic drug. Concomitant oral administration with propranolol or diltiazem can reduce their bioavailability and might reduce their therapeutic effects. Because of its action on the thyroid

Table 4: Interaction of common cardiac medicines with food & chemical: (Pronsky, Z. M., 2006).

Drug	Possible interaction with food
Beta Blockers (Antihypertensive) Atenolol, Carvedilol ,Metoprolol	• Avoid natural licorice. Take 2 hours before or 6 hours after calcium supplements and/ or orange juice. Calcium salts may decrease absorption.
Chlorothiazide ,Furosemide, Hydro-chlorothiazide,	• Increases excretion of electrolytes (potassium, magnesium and calcium). May need to supplement losses. Avoid natural licorice. Caution with calcium &/or vitamin D supplement.
Statins, HMG-CoA Reductase Inhibitors (Antihyperlipidemic) Simvastatin, Rosuvastatin, Atorvastatin	• Avoid alcohol, grapefruit juice and related citrus. Do not take some with high doses of niacin. Separate fiber, pectin and oat bran from drug by several hours.
Vasodilators, also known as nitrates (Antihypertensive) Isosorbide dinitrate, Nesiritide, Hydralazine, Nitrates and Minoxidil	• Limit alcohol. Decreased sodium and calcium intake may be recommended. Avoid natural licorice.
Anticoagulants Warfarin ,Enoxaparin ,Heparin	• Interacts with vitamin K; keep levels in diet consistent, caution with vitamin E and alcohol intake. Avoid or limit garlic, ginger, ginkgo, ginseng, green tea and avocado. • Barbiturates & phenytoin accelerates warfarin degradation in liver, reducing its efficacy. • Metronidazole *& Co*-trimoxazole, ***Cimetidine*** decrease warfarin degradation increasing its efficacy. • *Amiodarone, Allopurinol, cephalosporins* inhibit generation of vitamin K, accentuating warfarin potency.
Antiplatelet Agents Aspirin, Ticlopidine, Clopidogrel, Dipyridamole	• Avoid natural licorice. Take 2 hours before or 6 hours after calcium supplements.
Angiotensin Converting Enzyme (ACE) Inhibitors (Antihypertensive)	• Avoid salt substitutes. Caution with potassium (K) and magnesium (Mg) supplements. Limit alcohol. Decreased sodium (Na) and calcium may be recommended.
Diuretics	• Probenecid & lithium inhibit tubular excretion of thiazide diuretics.

(guggulsterone has thyroid-stimulating activity) caution should be used when administering with thyroid drugs (Dalvi et al. 1994).

6. Ginseng can inhibit the warfarin activity (Vaes and Chyka, 2000).
7. Grapefruit juice is a CYP3A4 inhibitor. So, statins, CCB or clopidogrel which use CYP3A4 for their metabolism, will be reduced in bioavailability or activity if taken with grapefruit juice (Tachjian et al. 2010).

CONCLUSION

Polypharmacy is often prescribed during management of cardiac patients who are mostly sick. When options of other drugs are not available it is desirable to keep a close vigil on patient's vitals with help of ECG and INR. Patients need to be counseled about the complexity of situation.

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