Review Article

Drug Interaction – Cardiovascular Drugs

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Abstract

All the available drugs in one way or other help the recipient to ward off or cure a disease, but at the same time each drug carries simultaneously an unavoidable risk of causing certain adverse effects which may be tolerable or intolerable. The severity of adverse effect increases when many drugs are prescribed. Whether such combinations, intentional or unintentional, really benefit or harm the recipient, should be known to a prescriber. With this objective the present article reviews in detail the potential outcome of combination of cardiovascular drugs.

Key Words: Drug Interaction, Cardiovascular drugs, Anti hypertensives, statins

Introduction

A drug when administered to a patient can interact with a) body, b) food, c) another drug, d) alcohol, e) tobacco taken simultaneously.

Interaction with the body is referred to as the "action of the drug" and the effect produced along with all other above mentioned agents is called "drug interaction". The outcome of such interaction may or may not be beneficial.

Broadly, drug interaction may be classified as general and specific.

General Drug Interactions

1. Drug – Food interactions

Food can delay or increase the absorption of the drugs or may not have any impact on absorption at all. The list of some of the cardiovascular drugs the absorption of which is altered by food is given in table 1[1].

Grapefruit and many other citrus fruits having flavonoids like naringen & naringenin, furanocoumarins like dihydroxybergamotin inhibit intestinal CYP3A4 enzyme activity and hence the drugs that are metabolized by these enzymes will be elevated in plasma resulting in toxicity[2].

Table 1: Effect of Food on absorption of drugs

Decreased	Delayed	Increased	Unaffected
Atenolol Sotalol Verapamil	Diltiazem Isosorbide-5-mononitrate Nicorandil Nifedipine	Amiodarone Nifedipine Ticlopidine	Amlodipine Bisoprolol Hydrochlorothiazide Metoprolol succinate

2. Drugs & Alcohol

Drugs that inhibit aldehyde dehydrogenase such as Disulfiram will lead to accumulation of aldehyde intermediates which cause flushing, nausea, vomiting and sweating all of which can be dangerous in patients with coronary artery disease.

Isosorbide dinitrate and nitroglycerine will also cause such disulfiram-like reactions if they are taken along with alcohol. Moreover hypotension due to nitrates may be aggravated by the vasodilatory effect of alcohol.

Drugs such as aspirin, ranitidine and nizatidine inhibit pre-systemic metabolism of alcohol and may increase the total alcohol level in systemic circulation[3]. Therefore patients taking such medications should be advised not to drink alcohol.

Apart from disulfiram-like reactions, alcohol can also influence hepatic microsomal enzymes. Generally, acute alcohol intake will result in inhibition of these enzymes, whereas chronic intake will stimulate the enzyme activity. Acute alcohol intake may decrease warfarin metabolism and cause bleeding but chronic alcohol ingestion may increase warfarin metabolism and precipitate coagulation.

3. Tobacco – drug interactions

Tobacco contains polyaromatic hydrocarbons (PAH) and nicotine. PAH is in general a hepatic microsomal enzyme inducer, especially CYP1A2 substrates. Enzyme induction increases the metabolism of coadministered drugs and hence smokers require higher dosage.[4]

Nicotine can interact with beta blockers. The sympathetic stimulation of nicotine may blunt the action of beta blockers

4. Drug – Drug interactions

When a drug is given along with another drug three possible effects can occur apart from the desired pharmacological effect, for which the drugs are administered. One drug can increase or decrease or may not affect the response of another drug. When a drug increases or facilitates the action of the other drug it is called synergism. Drugs are combined intentionally to get the synergistic effect.

For example, when calcium channel blocker Amlodipine is given along with hydrochlorothiazide, hydrochlorothiazide increases the antihypertensive effect of Amlodipine by causing elimination of sodium and water. WHO recommends such scientific and rational combinations.

Drug Interaction: Cardiovascular Drugs

The drugs prescribed for common cardiovascular diseases like hypertension, ischemic heart disease and congestive cardiac failure and arrhythmias are:

1. Diuretics
2. Sympathetic blockers
3. Calcium channel blockers
4. ACE inhibitors
5. Angiotensin receptor blockers
6. Nitrates
7. Anti platelet drugs
8. Hypolipidemic drugs
9. Digoxin
10. Adenosine

Most of the patients have concurrently other diseases such as diabetes, bronchial asthma and peptic ulcer. In such a situation in addition to cardiovascular drugs, antidiabetic, anti asthmatic and anti ulcer drugs have to be co prescribed. Hence, the number of drugs each patient has to take invariably will be more than 5. It is estimated that for patients taking 2-5 drugs daily the incidence of a potential drug interaction is 19%. This rises to over 80% for those taking 6 or more drugs.[5] It is reported that 20% of hospital admissions are due to drug - drug interactions[6]. The possible drug interactions that can occur with these groups of drugs can be any of the following:

Diuretics:

Diuretics facilitate the effect of co administered antihypertensive drugs. In the process they also cause electrolyte and metabolic disturbances.

The most important electrolyte imbalance is hypokalemia especially with loop diuretics like furosemide. Digoxin also causes hypokalemia. A patient with congestive cardiac failure would be receiving digoxin and diuretic, both can increase hypokalemia resulting in arrhythmia. Hence hypokalemia should be watched for and ECG taken at timely intervals can help prevent hypokalemia, arrhythmia and muscle weakness.

It is well known that potassium sparing diuretics (spironolactone, triamterene and amiloride) when given with ACE inhibitors can result in hyperkalemia.

Though it is uncommon to use non-selective β blockers, β blockers can also cause hyperkalemia by decreasing the cellular uptake of potassium and decreasing aldosterone level. When given with potassium sparing diuretics the chance for hyperkalemia is increased. [7]

β blockers:

β blockers like atenolol, metoprolol are combined with non-dihydropyridine calcium channel blockers like verapamil and diltiazem in the treatment of hypertension, ischemic heart disease and tachyarrhythmia. Both the groups of drugs decrease SA nodal and AV nodal activity and also inhibit myocardial contraction.

When a hypertensive patient is on antidepressant therapy, the antidepressant action can be blunted by β blockers which can enter the CNS (lipophilic drugs like propranolol and metoprolol).

When a patient is on anti diabetic drugs, β blockers including cardio-selectives can mask the warning signs and symptoms of hypoglycemia such as sweating, tachycardia and tremor. Hence β blockers should be used carefully in diabetics.

α blockers:

The anticipated side effect of α blocker is hypotension. When the patient is on repeated use of a nasal decongestant, the α agonist in the decongestant may decrease the action of α blocker and BP may not decrease .

It is reported that α1 blocker can cause fluid retention and if the patient is on either NSAID or steroid, fluid retention may be aggravated blunting the antihypertensive effect.

Calcium channel blockers:

The interaction between calcium channel blocker and β blocker has been discussed above. Amlodipine can cause pedal edema which can be reduced by the co administration of a thiazide diuretic like hydrochlorothiazide.

ACE inhibitors: (ACEI)[8]

Antacids may reduce the bioavailability of ACEI. It is well known that hyperkalemia can be caused due to simultaneous administration of ACE inhibitors and potassium sparing diuretics.

Some case reports link ACE inhibitors with the induction of lithium toxicity. Co administration of lithium should be undertaken with caution, and frequent monitoring of lithium concentration is recommended with all ACE inhibitors.

ACEI may increase the plasma level digoxin and lead to digoxin toxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) may attenuate the haemodynamic actions of ACE inhibitors and also they increase serum potassium as well as reduce the renal excretion of ACE inhibitors.

There is a little information available on the pharmacokinetic interaction with ACE inhibitors and cyclosporine, but caution should be exercised when they are used together.

Simultaneous administration of tetracycline with quinapril hydrochloride reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in quinapril tablets. This interaction should be anticipated if quinapril hydrochloride is co prescribed with tetracycline or other drugs that interact with magnesium.[9]

The interaction between enalapril and glibenclamide has been studied by Rave K et al. They have reported higher incidence of hypoglycemic episodes in patients given both enalapril and glibenclamide/insulin. ACE inhibitors may cause a temporary increase in the insulin sensitivity, which can lead to an increased risk of hypoglycemia. [10]

Angiotensin receptor blockers:

ACE inhibitors and ARBs should not be combined as there is a risk of hypotension, hyperkalemia and renal failure. Renal parameters and electrolytes should be checked regularly.

Nitrates:

Nitrates can decrease the effect of sumatriptan and other triptans in migraine. The triptans cause vasoconstriction of cerebral blood vessels whereas nitrates cause vasodilatation. Hence when a patient takes both the drugs together nitrates may blunt the action of triptans.

Digoxin interactions:

Aminosalicylic acid such as mesalazine and antacids decreases the effect of cardiac glycosides due to decreased GI absorption of digoxin. Muscle relaxants may increase the muscle weakness and chance of cardiac arrhythmias due to hypokalemia. Erythromycin and tetracycline increase digoxin level in blood leading to toxicity.

Hepatic microsomal enzyme inducers like phenytoin and rifampin induce the metabolism of digoxin. Hence dosage adjustment has to be made when digoxin is given to patients on treatment for epilepsy or tuberculosis.

Digoxin clearance is decreased by verapamil, diltiazem, cyclosporine, itrakonazole, quinidine, propafenone, and this may lead to digoxin toxicity. Corticosteroids may potentiate digitalis induced arrhythmias by causing hypokalemia.

Statins:

The major adverse effect of statins is myopathy. Concomitant use of drugs that diminish statins metabolism is associated with increased myopathy and rhabdomyolysis.

The most common interactions occured with fibrates, expecially with gemfibrozil, cyclosporine, digoxin, warfarin, macrolide antibiotics, mibenfradil and azole antifungals. These interactions result in increased plasma concentrations of statins and their metabolites.[11] The dose of statins should not be more than 10-20 mg per day when the patient is on any microsomal enzyme inhibitor.[12]

Consuming grape fruit juice should be avoided during statin therapy. Statins, especially, fluvastatin may affect coumarin anticoagulation and increase the risk of haemorrhagic events. Patients who receive warfarin should have INR monitored before starting statins and regularly throughout treatment. However, as pravastatin is not metabolised by cytochrome P450, warfarin interaction is of less importance. [12]

Rosuvastatin is also not associated with cytochrome P450 interactions. But cyclosporine may be avoided with rosuvastatin. HIV protease inhibitors strongly increase exposure to rosuvastatin and are not recommended for combination use. Antacids reduce rosuvastatin plasma levels.[12] Statins and leflunomide when given together the hepatotoxicity may be aggravated hence should be given cautiously. [13]

Cardiovascular drugs and herbal medicines:

Izzo A & Ernst E have reported that St John's wort (Hypericum perforatum) lowers blood concentrations of digoxin, warfarin, cyclosporine, amitriptyline, indinavir, and theophylline and reduce their efficacy. St John's wort can cause intermenstrual bleeding when taken with oral contraceptive pills.

Ginkgo (Ginkgo biloba) can interact with warfarin and cause bleeding and also blunt the action of thiazide diuretic.

Ginseng (Panax ginseng) lowers blood concentrations of alcohol and warfarin, and induces maniac if used concomitantly with phenelzine.

Garlic (Allium sativum) can reduce the blood level of warfarin.

Thus interactions between herbal medicines and cardiovascular drugs can occur hence physicians should know about the use of herbal products by their patients and the possibility of herb-drug interactions.[14]

Conclusion:

From this review it is evident that cardiovascular drugs will be lifesaving if combined wisely but if they are not rationally combined they can cause life threatening effects.

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