

Drug interactions of antihypertensive agents

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Introduction

Adverse drug-drug interactions may occur when a major therapeutic mechanism of one drug class (such as bradycardia with a beta blocker) is excessively exaggerated by the addition of another heart-rate slowing antihypertensive, such as verapamil. The most important interactions at the molecular level are those of the hepatic enzyme, cytochrome (CYP) 3A4. A classic example is the inhibitory effect of grapefruit juice in large amounts on CYP3A4, which decreases the breakdown of the antihypertensive agent nifedipine, to produce hypotensive side-effects. Common beneficial drug interactions occur when the normal side-effect of one drug, such as potassium loss with the use of diuretics, is opposed by another drug, such as an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB).

The first type of drug interaction is when one of the normal actions of one drug becomes exaggerated, to become a side-effect. The second type of interaction is at a molecular level, when the two drugs are both

broken down by the same liver enzyme, e.g. amlodipine and simvastatin.

Table I summarises the notable drug interactions of each class of drug used to treat hypertension.

Beta blockers

The pharmacodynamic interactions of beta blockers can be predicted. Beta blockers depress the sinoatrial (SA) and atrioventricular (AV) nodes when combined with other negative inotropic agents (Table I). Those drugs that are metabolised by the liver, metoprolol, carvedilol, labetalol and propranolol,¹ are prone to hepatic interactions. Of this group, metoprolol and carvedilol are more frequently used. Metoprolol is metabolised by the hepatic CYP2D6 system, that is inhibited by paroxetine, a widely used antidepressant and selective serotonin reuptake inhibitor.² The hepatic system is also inhibited by propoxyphene, an opioid pain-relief agent, available in South Africa as Distalgesic[®], although it was recently withdrawn in the USA.³ Carvedilol is metabolised by the same system, with the same possible interactions.⁴

Table I: Drug interactions of antihypertensive drugs, classified according to drug class

Drug class	Drug interactions
Beta blockers	Bradycardia. Hepatic interactions for metoprolol, carvedilol (CYP2D6), labetalol, and propranolol. Bisoprolol and nebivolol eliminated by both liver and kidney, hence a lesser risk of hepatic interactions. No hepatic interactions for atenolol, nadolol, and sotalol.
Calcium-channel blockers	Bradycardia and heart block, with heart rate-reducing agents (verapamil and diltiazem). Amlodipine and nifedipine, hepatic interaction with simvastatin and atorvastatin.
Diuretics	Hypokalaemia opposed by concurrent ACE inhibitors/ARBs.
ACE inhibitors, ARBs and renin inhibitors	Hyperkalaemia opposed by concurrent diuretics.
Aldosterone blockers	During co-therapy with spironolactone or eplerenone for hypertensive heart failure, danger of hyperkalaemia.
Alpha blockers	Risk of fluid retention with heart failure opposed by concurrent diuretics.

Calcium-channel blockers

Amlodipine is most frequently used in hypertension therapy.⁵ However, a recent molecular interaction has been found with simvastatin, one of the most commonly used agents in the treatment of hyperlipidaemia.

Verapamil

Verapamil is an antihypertensive agent that is also metabolised by high first-class liver metabolism using multiple components of the CYP450 system, including CYP3A4. The latter explains why verapamil increases the blood levels of several statins, such as atorvastatin, simvastatin and lovastatin. Caution should be taken when using verapamil, as it has similar interactions as those described for amlodipine.

Other drugs that interact with verapamil are the beta blockers. To avoid any hepatic pharmacokinetic interactions, verapamil is best combined with a hydrophilic beta blocker, such as atenolol or nadolol, rather than with those that are also metabolised in the liver, such as metoprolol, propranolol, or carvedilol.⁶

Diltiazem

Unlike verapamil, the effect of diltiazem on the blood digoxin level is often slight, or negligible.⁶ A haemodynamic interaction is expected with beta blockers. As with verapamil, but probably less so, diltiazem may inhibit CYP3A.

Nifedipine

Nifedipine is also broken down by the hepatic CYP3A4 system. This interaction should also lead to sensitivity to high doses of simvastatin. In large amounts, both cimetidine and grapefruit juice inhibit the CYP3A4 system. All the agents that inhibit CYP3A4 and thus the breakdown of nifedipine also potentially increase blood levels and antihypertensive effects.⁶ Conversely, phenobarbital, phenytoin, and rifampin induce the CYP3A4 system to metabolise nifedipine, so that blood levels should fall. Volatile anaesthetics interfere with the myocardial calcium regulation, and have inhibitory effects on cardiac contraction in addition to those of nifedipine.⁶

Amlodipine

Simvastatin has a hepatic interaction with amlodipine, as both are metabolised by the enzyme CYP3A4. The US Food and Drug Administration (FDA) has counselled that the two agents should not be used together if the simvastatin dose exceeds 20 mg per day.⁷ Logically, similar caution should extend to co-therapy of amlodipine with atorvastatin and lovastatin, as both of these are also metabolised by the same liver enzyme.

Diuretics

Loop diuretics, such as furosemide (Lasix®), and the thiazides, comprise the major diuretic subtypes. The thiazides are further subdivided into standard thiazides, such as hydrochlorothiazide, and thiazide-like agents, chlorthalidone and indapamide. Studies with outcome benefit have been conducted on both these thiazide-like agents. These include the Multiple Risk Factor Intervention Trial (MRFIT) with chlorthalidone,⁸ and the Hypertension in the Very Elderly Trial (HYVET) with indapamide.⁹ By contrast, outcome studies are lacking for hydrochlorothiazide.

Diuretic-drug interactions

The major side-effect of all diuretics is hypokalaemia, made worse by a low-potassium diet, or steroid co-therapy, or both.¹⁰ Conversely, a favourable drug-drug interaction is with angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs), which retain potassium. Antiarrhythmic agents that prolong the QT interval, such as class 1A or class 3 agents, including sotalol, may precipitate torsades in the presence of diuretic-induced hypokalaemia. Steroids may also cause sodium retention to antagonise the major effect of all diuretics, that of natriuresis. Probenecid may interfere with the effects of thiazides and loop diuretics by blocking thiazide transport into the proximal tubule.¹⁰ The nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the renal response to loop diuretics, presumably by interfering with the formation of vasodilatory prostaglandins. Hyperglycaemia is a class side-effect of diuretics, and is more marked in loop diuretics and at higher thiazide diuretic doses. This results in interference with the efficacy of anti-glycaemic drugs.¹⁰

Other antihypertensive drugs

The major drug interactions of the three major drug classes recommended by National Institute for Health and Clinical Excellence (NICE),⁵ namely calcium-channel blockers, diuretics, and ACE inhibitors/ARBs, have already been discussed, as have the interactions of the beta blockers.¹ Other drugs used to treat resistant hypertension include the aldosterone antagonists. There is a danger of hyperkalaemia when they are used together with an ACE inhibitor or an ARB. This danger also exists with the use of potassium supplements, and is particularly marked if there is reduced creatinine clearance.

ACE inhibitors

As a group, ACE inhibitors have a well-known association with potassium retention and an increased blood potassium level. This leads to a beneficial drug

interaction with diuretics, and the combination of an ACE inhibitor and a diuretic is regarded by NICE as a fundamental drug combination.⁵

Conversely, there is a potential problem in co-therapy when used with spironolactone or eplerenone. In this instance, the major danger is hyperkalaemia, and a lesser concern is an increase in serum creatinine.^{11,12} Potential red flags include prior use of potassium-retaining diuretics, a plasma creatinine level exceeding 220 µmol/l, or an estimated glomerular filtration rate less than 30 ml/minute/1.73m² of body surface area and a serum potassium exceeding 5 mmol/l.^{11,12} Nonetheless, under careful supervision, the combination of an ACE inhibitor with either of these two agents may give better results in the treatment of heart failure.

ACE inhibitors and aspirin or NSAIDs

Part of the antihypertensive mechanism of action of ACE inhibitors involves the formation of bradykinin, and thereby prostaglandins. These may play an important role in peripheral and renal vasodilation. Hence, in general, the NSAIDs (especially indomethacin) lessen the effectiveness of ACE inhibitors in hypertension.¹³ Sulindac may have less of an effect, and the ARBs seem to interact less, too. For practical purposes, there is no interaction with aspirin.

Renin inhibitors

Drug interactions for aliskiren are similar to those for ACE inhibitors or ARBs.

Alpha-adrenergic blockers

Fluid retention is a side-effect. Therefore, when used with diuretics, a beneficial drug-drug interaction should result.

Statins and antihypertensive agents

The interaction of simvastatin with the hepatic enzyme CYP3A4, as listed by the FDA, has led to the need to limit the doses of simvastatin used during co-therapy with certain antihypertensive agents as follows.⁷ Simvastatin is limited to 10 mg daily during co-therapy

with diltiazem and verapamil, and to a 20 mg daily limit when used during co-therapy with amlodipine. Another commonly used, but more expensive, statin, rosuvastatin, is cleared by CYP2C9, as is fluvastatin.

Grapefruit juice

Grapefruit juice inhibits hepatic CYP3A4. But how serious is this interaction? In patients on stable atorvastatin treatment, the addition of 300 ml grapefruit juice daily only slightly elevated serum atorvastatin concentrations, without having any effects on serum lipids, and without resulting in hepatic or muscular side-effects.¹⁴

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