ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Heinous Review On Inquiry Of Drug Interactions Among Hypertensive Patients Taking Antihypertensive Agents.

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ABSTRACT

Hypertension (HT), which is defined as a chronic elevation of systolic and/or diastolic blood pressure (BP), is in all probability the most common chronic disease today. Drug interactions occur when the effect of one drug is altered by the co administration of another. Such alterations may result either from changes in the drug's concentration (pharmacokinetic interaction) or from changes in the drug's effect independent of concentration (pharmacodynamics interaction). Several studies have shown age-related reduction in liver metabolism of many drugs. These changes significantly influence pharmacokinetics. Polypharmacy is common in the elderly. It is estimated that more than 40% of persons aged 65 or older use 5 or more, and 12% use 10 or more different medications. The previous studies which included younger hypertensive patients identified up to 48% of patients with potential interactions of high significance.[22] This difference in incidence of interaction is a consequence of comorbidity and polypharmacy which occur in elderly patients. Many studies emphasise the importance of monitoring of potential drug interactions in elderly patients with arterial hypertension. Fortunately, majority of these interactions can be managed by clinical and laboratory monitoring of patients or by dosage adjustments of one or both agents.

Keywords: Hypertension, drug interaction, pharmacokinetic interaction, pharmacodynamics interaction,

https://doi.org/10.33887/rjpbcs/2020.11.1.7

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ISSN: 0975-8585

INTRODUCTION

Hypertension (HT), which is defined as a chronic elevation of systolic and/or diastolic blood pressure (BP), is in all probability the most common chronic disease today. The main clinical significance of HT, which is not a disease in the usual sense of the word, lies on the future risk of vascular disease. Apart from various causes of HT, the most frequent case is the essential HT (up to 95%).[1,2] In the regulation of BP, there are different involving factors (sympathetic nervous system, kidney, hormonal systems), one of them being the composition of the diet. Thus, sodium, potassium, magnesium, lipids and total energy intake influence the control of BP.[3]

Drug interactions occur when the effect of one drug is altered by the co administration of another. Such alterations may result either from changes in the drug's concentration (pharmacokinetic interaction) or from changes in the drug's effect independent of concentration (pharmacodynamic interaction). 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).

Adverse effects of beta-adrenergic receptor blocking drugs can be divided into two categories:

- Those that result from known pharmacological consequences of /3-adrenergic receptor blockade.
- Other reactions that do not appear to result from /3-adrenergic receptor blockade.

Adverse effects of the first type include bronchospasm, heart failure, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud's phenomenon. Neurological reactions include depression, fatigue, and nightmares.

Elderly patients often exhibit an increased sensitivity to a large number of drugs , particularly to medications targeting the central nervous system. At the same time, sensitivity of β-adrenergic cardiovascular receptors is reduced. [4] Since over 50% of all patients aged 65 years or more take at least 5 drugs daily, plus an often unknown amount of over the counter medication, doctors need to be aware of potentially inappropriate medication (PIM) and potential drug-disease interaction (PDDI) in these patients. Aging is characterised by a progressive loss of functional capacities of most organs and reduction in homeostatic mechanisms. Reduction in renal function, particularly glomerular filtration rate, affects the drug clearance. Several studies have shown age-related reduction in liver metabolism of many drugs.[5] These changes significantly influence pharmacokinetics. On the other hand, pharmacodynamic changes in the elderly are commonly ascribed to alternation in the sensitivity to drugs, irrespective of changes in drug disposition.[6] Polypharmacy is common in the elderly. It is estimated that more than 40% of persons aged 65 or older use 5 or more, and 12% use 10 or more different medications.[7] It makes this population very susceptible to side effects of drug interactions since the risk of interactions increases exponentially with the number of drugs.[8] The incidence of potential drug interactions increases from 13% for two drugs to 82% for seven or more drugs.[9]

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

ISSN: 0975-8585

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.

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,[10] 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.[11] 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.[12] Carvedilol is metabolised by the same system, with the same possible interactions.[13]

Calcium-channel blockers

Amlodipine is most frequently used in hypertension therapy.[14] 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.[15]

Diltiazem

Unlike verapamil, the effect of diltiazem on the blood digoxin level is often slight, or negligible.[15] 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.[15] 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.[15]

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.[16] 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 thiazidelike agents. These include the Multiple Risk Factor Intervention Trial (MRFIT) with chlorthalidone,[15] and the Hypertension in the Very Elderly Trial (HYVET) with indapamide.[16] 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 cotherapy, or both.[17] 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.[17] 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 antiglycaemic drugs.[17]

Other antihypertensive drugs

The major drug interactions of the three major drug classes recommended by National Institute for Health and Clinical Excellence (NICE),[14] namely calciumchannel blockers, diuretics, and ACE inhibitors/ARBs, have already been discussed, as have the interactions of the beta blockers.[10] 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.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.[18, 19] Potential red flags include prior use

of potassiumretaining diuretics, a plasma creatinine level exceeding 220 mmol/l, or an estimated glomerular filtration rate less than 30 ml/minute/1.3ml of body surface area and a serum potassium exceeding 5 mmol/l.[18, 19] 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.[20] 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.[16] 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. 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 musclular side-effects.[21]

DISCUSSION

Some previous studies which included younger hypertensive patients identified up to 48% of patients with potential interactions of high significance.[22] This difference in incidence of interaction is a consequence of comorbidity and polypharmacy which occur in elderly patients. An emergency department study of patients aged 65 or older identified 31.1% incidence of potential interactions, by using a computer programme.[23] In general medical wards, the rate of potential drug interactions has been approximately 60% .[24] It is well known that NSAID can increase blood pressure and interfere with lowering effect of many classes of antihypertensive drugs. Even small rises in blood pressure due to therapy with NSAID may significantly increase cardiovascular risk, if sustained over a long time.[25, 26] According to the published data of many studies, interaction between NSAID and cardiovascular drugs are the most common interactions in the elderly associated with adverse patient outcomes.[27, 28] Many hypertensive elderly patients require chronic pain relief. In these patients paracetamol is the safest alternative to NSAID.[29] By adherence to these guidelines, we could probably improve treatment of arterial hypertension and prevent many adverse reactions of NSAID. The most common interaction in many studies was the interaction between ACEI and thiazides or loop diuretics. ACEI have been the most commonly used class of antihypertensives in Croatia for many years, and they very often interact with other cardiovascular drugs.[30] For example, Radosevic et al. found that the most common potentially harmful drug combination in hospitalised patients was an ACEI with a potassium supplement.[31] Loop diuretics are more potent than thiazides, and more often cause hypovolemia and hyponatremia. That is why the risk of pharmacodynamic interactions is higher when loop diuretics are combined with other antihypertensive drugs compared to thiazides. Concomitant therapy with ACEI or angiotensin II receptor blockers and diuretics is of

key importance, and it has been proposed to start treatment of hypertension in diabetic patients with combination therapy in order to avoid postponement of effective treatment with the aim of normalising blood pressure.[32]

CONCLUSION

Pharmacists in every practice setting need to be vigilant in monitoring for potential drug-food interactions and advising patients regarding foods or beverages to avoid when taking certain medications. It is imperative for pharmacists to keep up-to-date on potential drug-food interactions of medications, especially today's new drugs, so that they may counsel properly. Many studies emphasise the importance of monitoring of potential drug interactions in elderly patients with arterial hypertension. Fortunately, majority of these interactions can be managed by clinical and laboratory monitoring of patients or by dosage adjustments of one or both agents. This is especially important in the case of concomitant therapy with different classes of antihypertensive drugs. In other cases changes in drug therapy should be considered. Computer-based screening could help pharmacists and physicians to recognise potential clinically significant drug interactions and avoid undesirable adverse events. The response to antihypertensive agents may vary among patients as well as in each individual patient, with potentially serious consequences, this being influenced by some interactions, either drug-drug or drug-food. Taking various and very different drugs (antihypertensive and others) is common and food shall be accompanied by the taking thereof. Food may affect the BA of the antihypertensive agents and in some specific cases this should be carefully considered.

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