

CLINICAL PHARMACOLOGY

DRUG INTERACTIONS WITH THE CALCIUM-CHANNEL BLOCKERS

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, food or by some environmental chemical agent. The outcome may be harmful if the interaction either increases the toxicity of the drug or results in a reduction in efficacy. However, drug interactions may also be useful, such as the deliberate co-prescription of drugs with the same effect for additive or even synergistic effect (e.g. combination antihypertensive agents from different classes). The elderly are most at risk of drug interactions as they take many medicines and have age-related declines in cardiac, hepatic and renal functions.

Drug interactions are classified as either pharmacokinetic or pharmacodynamic. *Pharmacokinetic interactions* involve drug absorption, distribution, metabolism or excretion. Most orally administered drugs are lipophilic and need to undergo metabolism to less lipid-soluble compounds, which are excreted in the urine or bile. Most drug metabolism occurs in the liver enzymes, with the first phase via the cytochrome P450 (CYP450) enzyme system. Drugs may be substrates, inducers and/or inhibitors of CYP450 enzymes. Cytochrome P450 is a large family of related isoenzymes; about 30 have been found in human liver tissue. One group of isoenzymes, CYP3A, is responsible for the metabolism of more than half the drugs that are metabolised by CYP450. A second important site of pharmacokinetic interaction is the drug transporter P glycoprotein. In the gastrointestinal tract P glycoprotein acts by pumping xenobiotics (including drugs) out of cells and back into the lumen. P glycoprotein is also expressed at sites of excretion where it enhances xenobiotic elimination. Some drugs inhibit P glycoprotein, which results in increased bio-availability and decreased excretion of drugs that are P glycoprotein substrates, while other drugs induce P glycoprotein, resulting in the opposite effect. *Pharmacodynamic interactions* are due to effects (either beneficial or harmful) of co-administered drugs. These interactions may be either antagonistic or additive/synergistic.

Pharmacokinetic interactions with the calcium-channel blockers (CCBs)

All the CCBs are substrates of the CYP3A isoenzyme family (as noted above, this is responsible for the metabolism of more than half the drugs that are metabolised by the CYP450 system). In addition to being substrates, verapamil and diltiazem are also inhibitors of the CYP3A isoenzyme family. Finally, verapamil and diltiazem also inhibit P glycoprotein.

Therefore there are two major pharmacokinetic mechanisms of interactions involving CCBs. Firstly, the levels of CCBs can be reduced or increased by inducers and inhibitors of CYP3A respectively. This may result in reduced or toxic effects of CCBs respectively. Secondly, verapamil and diltiazem can increase the levels of other drugs that are substrates of CYP3A and P glycoprotein. Some examples of these interactions are listed in Tables I and II.

Table I. Pharmacokinetic interactions that potentially affect levels of CCBs

Mechanism of interaction	Examples of interacting agents
CYP3A isoenzyme induction	
The metabolism of all CCBs is increased and higher doses may be needed to maintain the same therapeutic effect. Note that the effects of enzyme induction are variable and affect CCBs to different extents	Carbamazepine, phenytoin, barbiturates, nevirapine, rifampicin, pioglitazone
CYP3A isoenzyme inhibition	
The metabolism of all CCBs is decreased. CCBs should be avoided or started at low doses. Note that the effects of enzyme inhibition are variable and affect CCBs to different extents	Cimetidine, erythromycin,azole antifungals, HIV-protease inhibitors, grapefruit juice

It is important to note that inducers or inhibitors of CYP3A affect CCBs differently. For example, HIV-protease inhibitors (which inhibit CYP450) increase the levels of amlodipine more than diltiazem. Secondly, the effect of inducers or inhibitors varies widely in individuals. This is illustrated by the HIV-protease inhibitor-CCB interaction study alluded to – the median increase in diltiazem exposure (measured by area under the curve) was 26.5%, but in some individuals there was more than a 400% increase. Appropriate management of these pharmacokinetic drug interactions begins with an awareness of the problem. The importance of individual variability must be borne in mind as interactions that are considered mild to moderate may result in severe consequences for an individual patient. Particular attention should be paid to those interactions which result in increased levels of CCBs or other interacting CCB – in this context an alternative drug

Table II. Pharmacokinetic interactions with CCBs

Mechanism of interaction	Examples of interacting agents
CYP3A isoenzyme inhibition by verapamil and diltiazem Lower doses of interacting drugs may be needed to maintain the same therapeutic effect, and levels or effects closely monitored	Many drugs, e.g. ciclosporin, most HMG CoA reductase inhibitors, most benzodiazepines, buspirone, sildenafil
P glycoprotein inhibition by verapamil and diltiazem Lower doses of interacting drugs may be needed to maintain the same therapeutic effect, and levels or effects closely monitored	Digoxin, ciclosporin, fexofenadine, daunorubicin, doxorubicin, etoposide, vinca alkaloids

Table III. Pharmacodynamic drug interactions with CCBs

Mechanism of interaction	Examples of interacting agents
Additive effect on hypertension Affects all CCBs	All antihypertensive drugs
Antagonistic effect on hypertension Affects all CCBs	NSAIDs, β_2 -agonists (oral), oral sympathomimetics
Additive negative chronotropic effect Affects verapamil and diltiazem	Digoxin, * β -blockers, amiodarone
Additive negative inotropic effect Affects mainly verapamil and diltiazem	β -blockers, flecainide

*Also has a pharmacokinetic interaction – see Table II.

should be used or the CCB started at a very low dose with frequent monitoring of effects (beneficial and toxic) and, where possible, therapeutic drug monitoring should be done (e.g. digoxin).

Pharmacodynamic interactions with the CCBs

CCBs can be divided into 2 classes: dihydropyridines (e.g. nifedipine, amlodipine) and non-dihydropyridines (verapamil and diltiazem). There are important differences in the cardiovascular effects of the 2 classes. Both classes reduce peripheral vascular resistance by vasodilatation. Both also inhibit cardiac muscle contraction (negative inotropism), but this effect is more pronounced for the non-dihydropyridines.

The non-dihydropyridines inhibit the SA and AV nodes (negative chronotropism) and lower heart rate – making them useful agents for supraventricular tachycardias. These different effects in the CCB classes result in different propensities for pharmacodynamic interactions (Table III).

Appropriate management of pharmacodynamic drug interactions once again begins with an awareness of the problem. The most important pharmacodynamic interactions occur with verapamil and diltiazem, both of which are negatively inotropic and chronotropic. Drugs which share these effects, notably the β -blockers, should be avoided or used with caution. Alternatively a dihydropyridine CCB can be used.

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Drug interactions are classified according to the underlying mechanisms: pharmacokinetic (affecting absorption, distribution, metabolism and excretion) and pharmacodynamic (shared drug effects, either beneficial or toxic). The elderly are particularly susceptible to drug interactions as they often are prescribed multiple drugs and have reduced hepatic and renal function. All CCBs are metabolised by the cytochrome P450 system (specifically the common drug-metabolising isoenzyme CYP3A), and their levels may be reduced or increased by co-administration with cytochrome P450 enzyme inducers or inhibitors respectively. In addition, verapamil and diltiazem (but not the other CCBs) are inhibitors of the CYP3A isoenzyme as well as the key drug transporter, P glycoprotein, resulting in increased levels of drugs that are substrates of either system. The most important pharmacodynamic interactions occur with drugs that share the negative inotropism and chronotropism of verapamil and diltiazem, notably the β -blockers.

Recommended reading

DuBuske LM. The role of P-glycoprotein and organic anion-transporting polypeptides in drug interactions. *Drug Saf* 2005; **28**(9): 789-801.
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