CALCIUM ANTAGONISTS – DRUG INTERACTIONS

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INTRODUCTION

Calcium antagonists are a group of compounds with diverse structures (Figure 1), that are now available for use in many diseases. Verapamil, nifedipine, diltiazem, are commonly prescribed; nitrendipine, gallopamil, nicardipine, lidoflazine, and tiapamil are less commonly prescribed and others are under development. The adverse effects of this class of drugs have been described, and reports of drug-drug interactions are appearing frequently.

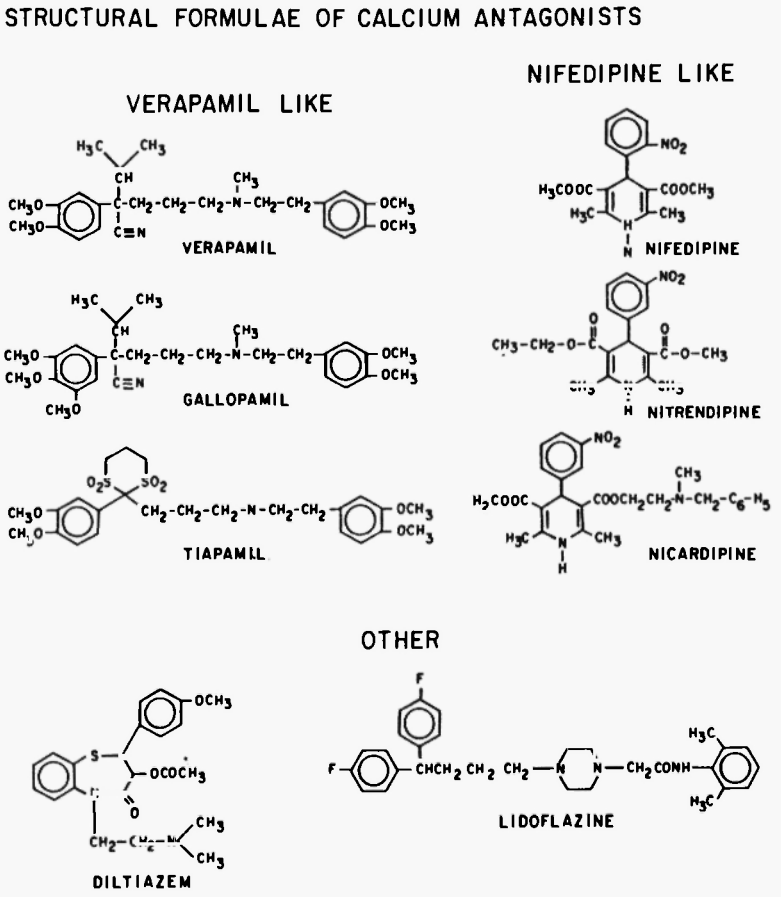

Figure 1. Structural formula of calcium antagonists.

The pharmacological actions produced by these drugs involve their effect on the calcium channels (or slow channels) located in cardiac

tissues such as the sinoatrial (SA) and atrioventricular (AV) nodes and peripheral or coronary vascular smooth muscle. Contraction in myocardial and vascular smooth muscle occurs by an increase in cytosolic Ca^{++} concentration /1/. There are two primary channels thought to be responsible for this increase in intracellular Ca^{++}: an electrical potential dependent channel and a receptor-operated channel. Calcium antagonists block both pathways /2,3/ and reduce transmembrane Ca^{++} influx into the excited muscle. In the heart, *in vitro* these drugs depress phase 4 depolarization in the SA and AV nodes. However, because of their ability to produce peripheral arteriolar vasodilation the effects of the calcium antagonist *in vivo* are different than *in vitro* /4-6/. The potency of these drugs according to their ability to produce peripheral vasodilation is: nifedipine > verapamil > diltiazem. These combined properties will produce changes in cardiac rhythm, preload, afterload, contractility and coronary blood flow.

Calcium antagonists are a heterogenous group of drugs. Individual agents within the group have a variable degree of selectivity for cardiac muscle and AV conduction as well as the peripheral and coronary vasculature. Generally calcium antagonists produce negative chronotropic and inotropic effects. The overall spectrum of clinical efficacy of calcium antagonists is similar to that of beta-blockers: both are antianginal agents, antiarrhythmic agents, antihypertensive agents, reduce coronary artery spasm and relax peripheral arterioles /4/.

The clinical pharmacology of verapamil, nifedipine and diltiazem is summarized in Table 1. Verapamil, a papaverine derivative, undergoes extensive hepatic biotransformation /7/. An active metabolite, norverapamil, produced by O-demethylation has about 20% of the activity, whereas an inactive metabolite is produced by N-dealkylation. Most of the drug is excreted in the urine as conjugated metabolite (70%), and in the faeces (15%) with less than 5% eliminated unchanged. In healthy subjects, total body clearance has been reported to range from 0.5 - 0.87 liter/minute and the volume of distribution (Vd) ranges from 112 - 380 liters. The drug is highly protein bound (90%) and elimination half-life (t 1/2) ranges from 1.8 to 5.3 hours. Verapamil is rapidly and completely absorbed after oral administration; however, systemic bioavailability is only 10 - 35% due to an extensive first-pass hepatic extraction /1,4,8/.

Nifedipine is approximately 90% absorbed following an oral dose, but a first-pass hepatic extraction reduces the systemic bioavailability

to 65 - 70%. Peak serum concentrations occur within two hours after an oral dose and within ten minutes of a sublingual dose. The drug is metabolized by oxidation to inactive compounds which are eliminated primarily by the kidney (70%). The serum concentration inversely affects the degree of protein binding, which ranges from 92 - 98%. The elimination half-life is 1.8 - 5.8 hours /9/.

Diltiazem is approximately 90% absorbed from the gastrointestinal tract, but according to Phiepho et al /10/, a first-pass effect reduces the systemic bioavailability to 45 - 67%. Peak serum concentrations occur within one hour following ingestion or three hours after a sustained release tablet. Diltiazem is extensively metabolized to five metabolites by several pathways including: deacetylation, N-demethylation and O-demethylation. Less than 4% is eliminated unchanged in the urine. The major metabolite, desacetyldiltiazem represents 15 - 35% of the administered dose and has 40 - 50% activity of the parent drug /1,8, 11/. Diltiazem is 80 - 85% protein bound but only 35 - 40% is bound to

TABLE 1. Clinical Pharmacology of Some Calcium Antagonists

	Verapamil	Nifedipine	Diltiazem
Absorption			
% Oral	90	90	90
% Bioavailable	10-35	65-70	45-67
Plasma half-life (hr.)			
Elimination t 1/2	1.8-5.3	4-5	4-6
Protein binding (%)	90	92-98	80-85
Metabolism	85% first-pass hepatic elimination to active and inactive metabolites	first-pass hepatic extraction to inactive metabolites	first-pass hepatic elimination to active and inactive metabolites
Excretion			
% Renal	70	70	35
% Faeces	15	15	65

albumin while the rest is bound to lipoprotein fractions and α_1 acid glycoprotein /12/. The elimination half-life of diltiazem is 4 - 7 hours /13/.

The pharmacodynamic, electrophysiologic and pharmacokinetic properties of the calcium channel blocking drugs can be influenced by a variety of other drugs. These interactions are the subject of the remainder of this review.

PHARMACOKINETIC INTERACTIONS

Altered Clearance

Digoxin and Verapamil

This combination has been shown to be useful in decreasing ventricular response rate in patients with chronic atrial fibrillation. When verapamil is added to a therapeutic regimen containing digoxin, induction of AV block can occur. Several clinical studies have documented significant increases in the steady-state plasma digoxin concentration when verapamil is co-administered with digoxin /8,14-17/, with the suspected development of digoxin toxicity /15/. Doering /18/ reported no drug interactions between verapamil and digoxin.

Klein et al /15/ reported that verapamil increased the serum digoxin concentration by 72% in patients with atrial fibrillation on stable doses of digoxin (0.25 mg/day). Other studies confirmed this finding but report a lesser increase in the serum digoxin concentration /16,19-21/. After one week of verapamil at a dose of 240 mg/day, healthy subjects on a maintenance dose of digoxin showed an increase of mean serum digoxin concentration from 0.21 to 0.34 ng/ml (60% elevation). These changes gradually subsided when patients remained on constant doses of the two drugs for 6 more weeks, and serum digoxin concentration decreased to 30% above control. This implies that verapamil alters digoxin elimination in long-term therapy /14/.

In another study the serum digoxin concentration increased from 0.6 ng/ml before verapamil to 0.84 ng/ml with 160 mg/day of verapamil and increased further to 1.24 ng/ml with 240 mg/day of verapamil /15/. Further increases in the verapamil dose do not lead to further elevations in serum digoxin concentration /22,23/. These data demonstrate that the digoxin-verpamil drug interaction is dose-dependent when using 240 mg/day or less of verapamil.

Four mechanisms could explain the interaction between digoxin and verapamil: 1) a decrease in renal digoxin clearance, 2) a decrease in nonrenal digoxin clearance, 3) a decrease in digoxin Vd by nonspecific binding of verapamil to the digoxin receptors in tissues, and 4) an increase in digoxin absorption from the gastrointestinal tract. Rigorous pharmacokinetic analysis of this drug interaction reveals that verapamil reduces digoxin total body clearance by 30 - 35% /14,16,24/. This reduction is due to impairment of both renal (20%) and extrarenal (60%) clearance /16/. Verapamil also decreases the apparent central Vd from

0.83 to 0.64 liter/kg /16/ and prolongs the biological half-life from 38.5 hours to 50.5 hours /16,23,24/. Changes in the digoxin Vd are not consistent and the role of Vd in this drug interaction is unclear /23-25/.

Klein et al /15/ demonstrated that an elevation in digoxin steady state concentration when verapamil is co-administered is due to a decrease in renal digoxin clearance. Because the glomerular filtration rate (creatinine clearance) is not affected by verapamil, it appears that verapamil inhibits the tubular secretion of digoxin /16/.

The renal tubular transport mechanism of digoxin in man accounts for 50% of the drug's renal clearance /26/. When digoxin(I^{125}) uptake is evaluated *in vitro* in kidney, heart and liver tissue slices, the renal uptake of digoxin is reduced by 15.8% when verapamil is added but at the same time uptake in the heart is unaffected. This suggests that the increase in serum digoxin concentration caused by verapamil is not caused or accompanied by displacement of digoxin from cardiac sites /27/.

The use of a combination of drugs – quinidine, digoxin and verapamil – given to manage supraventricular arrhythmias and atrial fibrillation is becoming more frequent. Serum digoxin concentration is increased by 53% when verapamil is added, and when quinidine is added to verapamil and digoxin there is an additional 66% serum digoxin concentration increase. In this case both verapamil and quinidine maintain their separate effects on digoxin pharmacokinetics /20/.

A substantial proportion of patients receiving digoxin may be temporarily exposed to potentially toxic plasma levels of digoxin (2.2 - 2.7 ng/ml) when verapamil is introduced. However, during long-term treatment in patients with normal renal function, the plasma digoxin elevation appears to subside/14/, which may explain the scarcity of adverse reactions reported by clinicians.

The clinical implications of the drug interaction are unclear. By increasing the availability of digoxin to cardiac tissue, verapamil could theoretically provoke digoxin toxicity. Klein et al /15/ showed a 14% (7 of 49 patients) occurrence of symptoms and ECG findings compatible with mild to moderate digitalis intoxication. Pedersen et al /23/ showed that a mild enhancement of the total inotropic effect occurred. Pedersen et al /24/ tried to document whether the increase in serum digoxin concentration from verapamil corresponded to a proportional increase in the risk of toxicity. He found a significant increase of intraerythrocytic Na^+ ($E\,Na^+$). Verapamil itself had no effect on $E\,Na^+$,

so this effect was attributed to increased digoxin concentration at the receptor level. Since E Na^+ concentration correlates with clinical signs of digoxin toxity /28/, the data indicate that verapamil is likely to increase the risk of digoxin induced arrhythmias.

In conclusion, digoxin-verapamil combination therapy is likely to increase the risk of digoxin toxicity, so caution should be taken when verapamil is administered to a fully digitalized patient. Until more is known, patients receiving both verapamil and digoxin should be carefully monitored for signs of digoxin toxicity and serum digoxin concentration should be monitored more closely than normal.

Digoxin and Diltiazem. Oyama et al /29/ studied 17 patients on digoxin therapy for chronic atrial fibrillation and showed that the mean values of steady state serum digoxin concentration were significantly increased from 36% to 50% during diltiazem (180 mg/day) co-administration. *In vitro* studies in mice have shown that the digoxin concentration in plasma and other tissues (brain, heart and liver) increase in the presence of diltiazem /30/. In healthy volunteers, diltiazem (90 mg/day) causes an increase in serum digoxin concentration at 3, 4, 6 and 12 hours after a single dose of digoxin, but this was not enough to influence the t $1/2\alpha$, t $1/2\beta$, or area under the curve (AUC) /31/.

Diltiazem produces decreases in renal digoxin clearance and in total body clearance which may be the reason in part for an increase in serum digoxin concentration /29,31,32/. The relatively small increase in serum digoxin concentration observed /31/, might be explained by the difference in a single dose study versus a steady state study /33/, or due to a dose dependent effect of diltiazem which has been observed in the digoxin-nifedipine studies done at steady state /22/ or single dose /19/.

Digoxin and Nifedipine. There are conflicting data available concerning this drug interaction. In recent studies by Belz et al /21,34/, the use of 30 mg/day of nifedipine was associated with a 40% increase in steady state serum digoxin concentration in healthy subjects. But Schwartz et al /35,36/ and a better controlled study by Pedersen et al /37/ dispute this data, showing that nifedipine has no overall influence on digoxin elimination in healthy subjects. While Belz et al /21,34/ did show a decrease in digoxin renal clearance, Pedersen et al /37/ showed that nifedipine significantly increased the extra renal clearance of a single digoxin dose from 1.09 to 1.45 ml/min/kg, while changes in the biological t½, Vd and the total body clearance of digoxin were small and insignificant.

Further studies are indicated to establish whether or not this drug interaction is clinically significant.

Digoxin and other Calcium Antagonists. Tiapamil (600 mg/day), nicardipine (60 mg/day) and gallopamil (150 mg/day),when co-administered with digoxin also result in increases in serum digoxin concentration /22,38/. As with other calcium antagonists, these drugs increase serum digoxin concentration by decreasing renal digoxin clearance.

It appears that the interaction between digoxin and calcium antagonist is greater with the verapamil-like substances than with the dihydropyridine (nifedipine-like) substances /38/.

ALTERED DISTRIBUTION AND PROTEIN BINDING

Calcium Antagonists and Phenytoin

Calcium antagonists are highly protein bound. *In vitro* binding studies have shown a significant decrease in verapamil binding in the presence of therapeutic concentrations of several weakly basic drugs (propranolol, diazepam, lignocaine and disopyramide) and to a lesser extent with salicylate, an acidic compound /39/. Ahmad /40/ showed that when nifedipine 30 mg/day was co-administered with phenytoin it caused phenytoin levels to increase to toxic concentrations (30.4 μg/ml) and 2 weeks after nifedipine discontinuation the phenytoin concentration was noted to be in the therapeutic range (10.5 μg/ml). Although specific binding studies were not performed, the author hypothesized that this effect of nifedipine may be due to release of phenytoin from protein binding sites. However, it seems that a decrease in metabolism is also a likely mechanism.

Altered Metabolism

Calcium Antagonists and Theophylline. Calcium antagonists are extensively metabolized in the liver by the cytochrome P-450 drug metabolizing enzyme system. The rate-limiting step in the hepatic elimination of calcium antagonists is hepatic blood flow /7/. Furthermore, calcium antagonists are likely to interact with agents which alter drug metabolzing enzyme systems or hepatic blood flow. Two case reports /41,42/ have shown an interaction between verapamil and theophylline /41/ and nifedipine and theophylline /42/. Patients in

these case studies had theophylline levels in the toxic range (27.9 μg/ml and 30.5 μg/ml respectively). Both calcium antagonists and theophylline have N-demethylation as a common metabolic step.

Calcium Antagonists and Cimetidine. Cho-Ming et al /43/ showed that cimetidine reduced verapamil clearance by 21% and half-life by 50% but found no significant change in Vd. In this study, cimetidine did not alter liver blood flow. Therefore, the decrease in verapamil clearance is not due to changes in liver blood flow or changes in Vd, but is likely due to the inhibition of the cytochrome P-450 systems.

Nifedipine and Quinidine. Green et al /44/ reported that a patient taking 324 mg of quinidine sulphate every 8 hours had serum quinidine levels of 2.6 μg/ml; when nifedipine (30 mg/day) was co-administered for 3 days, the serum quinidine concentration decreased to 1.6 μg/ml. Despite dosage increases of quinidine up to 2000 mg/day, the quinidine concentration failed to increase appropriately in the presence of nifedipine and remained low. After discontinuation of nifedipine therapy, the serum concentration of quinidine doubled without a change in the quinidine dosage.

PHARMACODYNAMIC EFFECTS

Calcium Antagonists and Antineoplastic Agents

Calcium antagonists have no antitumor activity themselves but have been found to potentiate the effects of cytotoxic agents such as vinca alkaloids and anthracyclines in murine tumors as well as *in vitro* human leukemia cell lines. Some cell resistance to vincristine or adriamycin has been attributed to the enhanced drug efflux. Studies with resistant tumor cells performed by various researchers /45-47/ revealed that verapamil increased vincristine and adriamycin accumulation in resistant and sensitive tumor cells and also enhanced these agents' cytotoxicity *in vitro*. Tsuruo et al /48/ also showed that diltiazem, nicardipine, niludipine and nimodipine had that same effect both *in vitro* and *in vivo*, while nifedipine had less effect. Diltiazem and nicardipine enhanced the cytotoxicity of vincristine in P388 cells by 7.8 and 4.3 fold respectively and adriamycin cytotoxicity by 27 fold. Yanovich et al /49/ found a five fold increase in daunomycin uptake in resistant

and sensitive P388 cell lines. Tsuruo et al. /47/ reported that the most effective therapeutic response in P388/vincristine bearers was obtained when vincristine and verapamil were administered at the same time.

These reports indicate that inherent resistance to vincristine and anthracyclines can be circumvented by calcium antagonists through inhibiting drug efflux. The mechanism is unknown. The clinical application of calcium antagonists to enhance drug cytotoxicity might be difficult because of the drug's coronary vasodilator activity.

Calcium Antagonists and Calcium

Boe et al /50/ demonstrated in dog hypoxic myocardial tissue that calcium sequestration after an injection of calcium chloride reached maximum accumulation after 10 minutes of reperfusion. The increase in Ca^{++} accumulation in ischemic myocardium was reduced by 31.5%, 82% and 39% when nifedipine was added at 0, 20 and 30 minutes of reperfusion. Calcium sequestration is highly correlated with irreversible intracellular changes /51/, and a decrease in Ca^{++} seqestration has been shown to improve left ventricular performance /52/.

In an isolated atrium of an adult rat heart the negative chronotropic effect of calcium antagonist agents was not reversed by increasing the Ca^{++} concentration in the surrounding media but did reverse the negative inotropic effect /53/. This is in agreement with Morris et al. /54/ who showed that intravenous Ca^{++} reversed verapamil's negative inotropic effect. When the calcium antagonists (verapamil, nifedipine) were incubated with different Ca^{++} concentrations (1, 3, 6 and 9 mMol/1), the chronotropic response was unaffected by the changes in Ca^{++} concentration between 1 - 3, but there was an enhancement of the negative chronotropic effect when Ca^{++} concentration was above three.

Calcium ions and the calcium antagonists produce opposite chronotropic effects when used individually but they interact synergistically. The mechanism of this paradoxical effect is unknown.

Effect of Acidosis on Calcium Antagonists

Briscoe et al. /55/ who studied the cat heart showed that lowering extracellular pH increased verapamil and nifedipine effects. While using either verapamil or nifedipine with decreasing pH (7.4, 6.8, 6.0), the change in dissociation constant (K_B) for verpamil illustrates that their sensitivity increased under acidotic conditions. This change in K_B

suggests that less Ca^{++} will bind to troponin due to the competitive interaction with calcium antagonists /56/. It is possible that during acidosis, such as occurs locally during myocardial ischemia, a partial inhibition of the slow Ca^{++} channel increases the sensitivity of calcium antagonists.

Calcium Antagonists and Halogenated Anesthetics

Marshall et al /57/ found that halothane co-administered with nifedipine in an isolated rat heart preparation caused a pronounced combined negative inotropic effect, which was confirmed by Kates et al /58/ when using isoflurane and verapamil in mongrel dogs. Kates's study is compatible with previous studies done in cats /59/ or intact dogs /60/. Both halothane and nifedipine exert their negative inotropic effects by a mechanism involving Ca^{++}. Halothane inhibits Ca^{++} influx through cell membranes /61/ and nifedipine inhibits the entry of Ca^{++} into the cell.

Clinical implications of the above are limited. However, these laboratory findings demonstrate that verapamil and nifedipine enhance the hemodynamic effects of isoflurane and halothane in a manner that needs to be considered when both drugs are given together.

Calcium Antagonists and Beta-Blockers

Combined therapy with calcium antagonists and beta-adrenergic blockers play a large role in the treatment of angina pectoris and hypertension. Drug interactions may occur with this combination. In fact, several reports have shown that the combination of calcium antagonists and beta blockers in humans may result in cardiac failure, hypotension, bradycardia and/or asystole /62-68/. In anesthetized dogs nadolol was found to be safe to use in combination with nifedipine, but not with tiapamil /69/. Tiapamil, a calcium antagonist structurally related to verapamil, was given with nadolol to dogs in which stenosis had been induced in the left circumflex coronory artery. This combination produced bradycardia, hypotension, decreased myocardial contractility and coronary blood flow and death. Saini et al /69/ concluded that fatal interactions could be expected with the combination of tiapamil and beta-blockers in patients with impaired ventricular

function because of additive cardiodepressant effects. Nifedipine may be safer to use than verapamil-like compounds (e.g. tiapamil) because of its lack of antisympathetic activity and little effect on atrioventricular conduction and refractoriness.

The hemodynamic and clinical effects of verapamil and propranolol in humans with angina pectoris has been reviewed by Packer et al /70/. The authors concluded that in patients with preserved left ventricular function, decreases in ejection fraction of more than 5% can occur (which may produce congestive heart failure) in those patients taking large doses of propranolol from 160 to 1280 mg daily (mean 502 mg), and 120 mg of verapamil orally at 6 to 12 hour intervals. Smaller doses of propranolol 40-480 mg daily (mean 160 mg) in combination with verapamil given intravenously (0.025 to 0.1 mg/kg bolus, 0.005 mg/kg/min continuous infusion for 45 minutes) had little effect on cardiac performance. The dose response interaction was thought to be due to the requirement of large propranolol doses to lessen the beta adrenergic reflexes enough to allow for unopposed negative inotropic effects by verapamil. Clinical benefits of the verapamil propranolol combinations have been observed in patients with preserved left ventricular function and in patients with severe left ventricular dysfunction, but a high incidence of side effects (i.e. hypotension, cardiac failure, bradycardia, junctional rhythm) occurred in patients with severe left ventricular dysfunction. Intravenous verapamil was also found to be safe to use in patients on low dose (160 mg/day) chronic propranolol therapy if severe left ventricular dysfunction, relative hypotension, bradyarrhythmia or conduction abnormalities had not occurred with previous propranolol use /71/. The combination of nifedipine with propranolol and atenolol and diltiazem with propranolol have also been shown to be both beneficial and safe /72-74/.

A study by Harmsen et al /75/ examined a physiological mechanism for the beneficial effect they found in ischemic rat myocardium from the combination of nifedipine and propranolol. They conclude that this effect is primarily due to ATP-sparing properties of nifedipine which can be augmented by propranolol.

The combination therapy of calcium antagonists and beta-adrenergic blockers have also been found to be of benefit in the treatment of hypertension. Ekelund et al /76/ studied metoprolol and nifedipine use during rest and exercise in hypertensive males and found the antihypertensive effect potentiated by the use of both drugs without

adverse reactions. Opie et al /77/ found the same results in the acute and long-term use of atenolol and nifedipine. The authors also found the acute response would predict the long-term response to the combination.

Christensen et al /78/ studied the use of nifedipine in patients taking metoprolol, atenolol, timolol and propranolol for hypertension. Nifedipine addition to the therapy in patients whose hypertension was not controlled with beta-blockers reduced both systolic and diastolic blood pressures (average maximal reduction 30/22 mmHg). Blood pressure reduction from the combination was due to the lack of parasympathetic tone which mediates the response to heart rate. Renal blood flow was maintained with uricosuria and diuresis occurring with the above combinations.

In conclusion, co-administration of calcium antagonists and beta-adrenergic blockers in patients with angina pectoris or hypertension is of therapeutic benefit in those with preserved left ventricular function (ejection fraction greater than 30%). In patients with severe left ventricular dysfunctions and/or atrioventricular conduction diseases the combination should be avoided until further studies are performed.

Calcium Antagonists and Asthmatic Patients

Because of the role of calcium in smooth muscle contraction, calcium antagonists could directly affect bronchial smooth muscle and theoretically potentiate the action of β_2-adrenoceptor agonists /79/. Patients received oral nifedipine with either intravenous terbutaline or inhaled terbutaline. This study found a small potentiating effect of nifedipine on β_2-adrenoceptor-mediated bronchorelaxation but no effect on the resting bronchial tone. This potentiation occurred without any increase in tremor, but caused a significant increase in heart rate and decrease in diastolic blood pressure.

The effect of inhaled verapamil on histamine bronchoconstriction was studied in anesthetized dogs by Krivoy et al /80/. The results showed that large doses of verapamil (approximately 0.5 mg/kg) produced a significant increase in total lung resistance. This unexpected result is thought to be due to the inhibition of the efflux of calcium by histamine induction and/or the inactivation of the ATPase pump which is activated by calmodulin. The authors conclude that calcium antagonists must be used in much greater concentrations than is normal

practice to affect vascular smooth muscle in order to affect bronchial musculature.

Rolla et al. /81/ also found oral nifedipine beneficial in inhibiting deep inspiration-induced bronchoconstriction in symptomatically free asthmatics. This inhibition is thought to be due to the role of calcium in cholinergic bronchoconstriction which is blocked by calcium antagonists. This bronchoconstriction probably occurs because of lung irritant receptors that are abnormally sensitive to deep inspiration.

In contrast, both Patel et al /82/ and Malik et al /83/ found sublingual nifedipine to have little effect on histamine-induced bronchospasm in allergic asthmatic patients. The authors concluded that any effect seen was due to the inhibition of the calcium dependent release of mediators from mast cells and the calcium antagonist's effect on bronchial smooth muscle.

Calcium Antagonists and Hormones

Some hormones depend on translocation of extracellular Ca^{++} across a cell membrane for secretion and it is possible that interactions with calcium antagonists might occur. But Millar et al /84/ cautions readers that calcium antagonists probably affect calcium in the cells in other ways than just calcium translocation. Also, *in vitro* results may not be seen *in vivo*. All hormonal interactions below have already been outlined by Millar et al /84/. Important interactions identified in mostly animal models include effects on the hormones from the posterior and anterior pituitary, pancreas and adrenal cortex.

Gallopamil has been shown to inhibit the release of vasopressin and oxytocin *in vitro* (in rat neurohypophysis). Since this inhibition is reversed by calcium addition, it is thought to be due to blockade of transmembrane calcium influx. In toad bladders, verapamil blocks responses to antidiuretic hormone by affecting the calcium-adenylate cyclase interaction.

Verapamil inhibits secretion of prolactin from cloned pituitary cells from rats. In man, verapamil blocks the release of gonadotropins (LH and FSH) and thyrotropin and decreased basal levels of both LH and FSH. Nifedipine was found to have no effect on FSH, LH, thyrotropin or prolactin.

Several *in vitro* studies have shown nifedipine, verapamil, lanthanum, and diltiazam to inhibit insulin release, but results in humans have both found no inhibition /85/ and inhibition of insulin release /86-89/. Millar

et al /84/ speculated that calcium antagonists have clinically insignificant effects on insulin.

In vitro results in rat zona glomerulosa cells have shown verapamil to inhibit aldosterone responses to both secretagogues. In man, nifedipine decreases the responses to angiotensin II when infused acutely but not when given chronically. These interactions are thought to be due to calcium efflux inhibition and not uptake inhibitions.

In man, nifedipine given acutely stimulates renin release. Chronic administration of nifedipine or verapamil does not affect renin levels.

MISCELLANEOUS

Rabkin /90/ found in isolated rabbit heart that adriamycin reduces myocardial contractility (dp/dt) which was not altered by Ca^{++} concentrations ranging from 0.8 to 2.4 mM. This suggests that the acute negative inotropic effects of adriamycin are not mediated by Ca^{++}, even though a study /91/ suggests that the drug's cardiotoxicity involves myocardial cell Ca^{++}. This study also demonstrates that adriamycin further depresses myocardial contractility in the presence of verapamil pretreatment and low Ca^{++} concentration.

Captopril and nifedipine given together produced reduction in systolic blood pressure, larger than either drug alone /92/. These findings suggest that these drugs exert an additive hypotensive action by different mechanisms but the combination can be beneficial in the treatment of hypertension.

Bowles et al /93/ showed that amiodarone caused a significant reduction in the inotropic effect of verapamil and in some verapamil and amiodarone combinations caused sudden atrial arrest. Both drugs decreased atrial rate by direct effect on the sinoatrial node and produced an additive effect.

Verapamil and the ionic contrast media (meglumine and sodium diatrizoates) was found to cause direct inhibition of the conducting system and depression of the myocardial contractile state when administered together in dogs /94/. They also induced a significant increase in the PR interval from 150 to 600 msec and in some animals produced periods of second degree heart block. Nonionic contrast media (iohexol) caused no deleterious inotropic or dromotropic effects, and it should be used for coronary arteriography in patients taking verapamil. Both verapamil and diatrizoate salts affect the Ca^{++} within

the myocardium: diatrizoates bind Ca^{++} /95/ while verapamil blocks the Ca^{++} channels.

Formann et al /96/ found that nifedipine reduced myometrial contractions induced by oxytocin and prostaglandin $F_{2}\alpha$, which might be beneficial during spontaneous labour when an immediate uterine relaxation is required. However, since possible fetal reactions to nifedipine have not been investigated, its clinical use in pregnancy should be restricted.

Durant et al /97/ in a review of the literature and in an experiment in rabbit muscle showed potentiation of neuromuscular blockade by verapamil. Potentiation of neuromuscular blockade from succinylcholine and pancuronium occurred with what is thought to be therapeutic intravenous doses of verapamil. Two different explanations were postulated: 1) verapamil, by blocking post-junctional open acetylcholine-activated ionic channels, effects ionic conductance. Pancuronium and maybe succinylcholine have similar effects, or 2) verapamil may have a depressant action so when combined with presynaptic depressants pancuronium or succinylcholine it potentiates their neuromuscular blockade. Verapamil was shown to have no effect on alpha-bungarotoxin, a neuromuscular blocking toxin.

In a study of postsynaptic α_1, or α_2-adrenoceptors in pithed rats and cats and in ganglion-blocked rabbits, Van Zwieten et al /98/ found calcium antagonists to significantly reduce the pressor response of vascular postsynaptic α_2-adrenoceptors that had been stimulated with B-HT 920 and other agonists. The α_2 receptor-induced vasoconstriction was affected by calcium antagonists while α_1-adrenoceptors were not affected. Inorganic calcium blockers, such as cobalt, nickel, and manganese were also studied and found to selectively inhibit vasoconstriction of α_2-adrenoceptor stimulants. This interaction is thought to be due to the requirement of calcium ion influx across the membrane from the extracellular space for α_2-receptor stimulated vasoconstriction which is blocked by calcium antagonists.

Calcium antagonists, D600 (gallopamil), diltiazem and nicardipine, enhance the irreversible blockade by phenoxybenzamine of the histamine H_1 receptor in guinea pig caecum /99/. The authors speculate that calcium antagonists stabilize the calcium channel in the resting conformation which is more susceptible to phenoxybenzamine and/or this changed channel makes the histamine receptor more susceptible to phenoxybenzamine.

SUMMARY

Evaluations of drug interactions should be done with caution. One needs to be aware of the reported interactions and apply the information on an individual basis. This review may therefore serve as a guide to the more common drug interactions and when drug therapy should be monitored closely in clinical practice. Major drug interactions with calcium antagonists are summarized in Table 2.

TABLE 2. CLINICALLY SIGNIFICANT DRUG INTERACTIONS WITH CALCIUM ANTAGONISTS

Calcium Antagonist	Concurrent Agent	Interaction Reported	Special Conditions Required	Proposed Mechanism of Action	References
Nifedipine, Tiapamil, Verapamil,	Propranolol Practolol Timolol Nadolol	Cardiac failure, hypotension, bradycardia, asystole	1. Severe left ventricular dysfunction* 2. Previous relative hypotension, bradyarrhythmia or conduction abnormalities with propranolol. 3. Large doses of propranolol (160-1280 mg daily, mean 502 mg)	Additive cardiodepressant effects. Requirement of large propranolol doses to lessen the beta adrenergic reflexes enough to allow for unopposed negative inotropic effect by calcium antagonists.	68-71
Verapamil	Digoxin	Verapamil increases serum digoxin concentration by 30-70% and both therapeutic and toxic effect of digoxin have been increased.	None	Verapamil reduces both renal and non-renal clearance	14, 15, 16

TABLE 2. Cont. CLINICALLY SIGNIFICANT DRUG INTERACTIONS WITH CALCIUM ANTAGONISTS

Calcium Antagonist	Concurrent Agent	Interaction Reported	Special Conditions Required	Proposed Mechanism of Action	References
Diltiazem	Digoxin	Diltiazem increases serum digoxin concentration by 20-30%, digoxin toxicity was not seen	None	Diltiazem reduces renal and non-renal clearance	29, 31, 32
Diltiazem Nicardipine	Vincristine Anthracyclines	Potentiates effects of the cytotoxic agents	Cell resistance to cytotoxic effects of vincristine and anthracyclines	Inhibiting vincristine and anthracycline efflux	45-49

*(ejection fraction less than 30%)

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