Calcium channel blockers

See also Individual agents

GENERAL INFORMATION

The calcium channel blockers block the movement of calcium across L-type calcium channels. The main drugs that share this action are verapamil (a phenylalkylamine), diltiazem (a benzthiazepine), and the dihydropyridines, which include amlodipine, darodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, and nitrendipine. Other agents, for example prenylamine and lidoflazine, are now rarely used, and perhexiline, having failed to reach the market at all in some countries, was withdrawn in the UK after continuing concerns about its safety [1].

Mibefradil blocks T type calcium channels; it was withdrawn within 1 year of marketing because of multiple drug interactions, emphasizing the need for rigorous drug assessment before release and the importance of postmarketing surveillance of new drugs [2].

The properties of these drugs vary widely [3]. Nifedipine is said to have little negative inotropic effect and no effect on the atrioventricular node; verapamil is a potent cardiac depressant, with a marked effect on the atrioventricular node; and diltiazem has less cardiac depressant effect but inhibits atrioventricular nodal activity.

Controversy has surrounded the use of calcium channel blockers in the treatment of hypertension [4] and ischemic heart disease [5], with evidence for an association with unfavorable coronary outcomes compared with other therapies. Most of the evidence comes from the use of short-acting formulations, especially short-acting nifedipine. The hypothesis put forward to explain these findings was that short-acting formulations cause reflex activation of the sympathetic nervous system [6]. Further observational studies showed that these drugs were also associated with gastrointestinal hemorrhage [7] and cancer [8]. Claims of conflicts of interests amongst authors were published [9], often amid heated debate. Further evidence against the short-acting calcium channel blockers in hypertension has been forthcoming [10,11] and a worse than expected outcome with respect to coronary outcomes in diabetic patients has fuelled the debate [12]. Further evidence of gastrointestinal bleeding has been published [13], but there is evidence against a link with cancer [14]. All these scares have undoubtedly reduced the standing of this class of drugs in the eyes of physicians.

That calcium channel blockers are effective in relieving the symptoms of angina pectoris is beyond doubt. However, the Angina and Silent Ischemia Study [15], in which nifedipine, diltiazem, and propranolol were compared with placebo in a crossover study, produced conflicting results. Only diltiazem improved treadmill exercise time and only propranolol convincingly reduced the number of silent ischemic episodes during ambulatory monitoring. These findings are hard to explain [16]. Beta-blockers may be cardioprotective and therefore preferable to calcium channel blockers [17]. The clinically significant deterioration seen in patients with impaired left ventricular function taking calcium channel blockers is important, as many patients with angina have previously had a myocardial infarction or have poor left ventricular function. Calcium channel blockers cannot be assumed to be safe second-line drugs for angina in patients with poor cardiac reserve, although newer agents may prove to be safer [18].

Calcium channel blockers are very effective in controlling variant angina, and are often used during coronary angioplasty and after coronary artery surgery. They are also useful in patients who are intolerant of beta-blockers [19], or who have a poor response to nitrates, or who have concurrent hypertension.

General adverse effects and adverse reactions

Although they are chemically heterogeneous, many adverse effects and reactions are common to all calcium channel blockers, predictable from their pharmacological actions. Calcium plays a role in the functions of contraction and conduction in the heart and in the smooth muscle of arteries; drugs that interfere with its availability (of which there are many, the calcium channel blockers being the most specific) will therefore act in all these tissues. A few idiosyncratic and hypersensitivity reactions have also been reported with individual calcium channel blockers.

Throbbing headache, facial warmth and flushing, and dizziness are minor complaints associated with the use of calcium channel blockers; these effects are believed to be caused by inhibitory actions on smooth muscle [20]. Palpitation, muscle cramps, and pedal edema also occur [21–27]. Dizziness, facial flushing, leg edema, postural hypotension, and constipation have been reported in up to one-third of patients. They are rarely severe and often abate on continued therapy. More serious adverse effects, mainly those affecting cardiac conduction, are much less common, and only rarely is withdrawal necessary.

ORGANS AND SYSTEMS

Cardiovascular

Cardiac failure

Although acute hemodynamic studies have suggested that calcium channel blockers can be beneficial in cardiac failure [28], long-term treatment has been associated with clinical deterioration. Calcium channel blockers should therefore be prescribed with caution for patients with impaired cardiac function, who should be regularly reassessed; treatment should be withdrawn if the signs or symptoms of cardiac failure appear. In some cases heart failure is predictable, as in the case of a patient with aortic stenosis who developed left ventricular failure after treatment with nifedipine [29]. Increased sympathetic activity can also compensate for the myocardial suppressant effects of calcium channel blockers, and the combination of these drugs (particularly verapamil) with beta-adrenoceptor antagonists has therefore given cause for concern in the past, although this combination is now considered relatively safe for the majority of patients with normal cardiac function [30–32].

Myocardial ischemia

There have been many studies of the efficacy of calcium channel blockers in early and late intervention in myocardial infarction [33]. These studies have failed to show convincing benefits. Indeed, in the nifedipine intervention studies there was a consistent trend towards higher mortality in the treated patients than in those taking placebo. A study in which patients were randomized to placebo or nifedipine within 48 hours of admission was terminated after 1358 patients had been recruited, because mortality at 6 months was 15.4% on nifedipine and 13.3% on placebo [34].

It has been argued that dihydropyridine calcium channel blockers, which increase heart rate, can all increase the risk of death and reinfarction [35,36]. Early beneficial results with diltiazem in patients with non-Q-wave infarction [37] were not confirmed in the Multicenter Diltiazem Postinfarction Trial [38]. In patients with pulmonary congestion, diltiazem was associated with an increase in cardiac events, and there was a similar result in patients with low ejection fractions. However, verapamil does appear to reduce reinfarction [39], a benefit that is more marked in those without heart failure [40]. Nifedipine may also have a detrimental effect in unstable angina; it certainly appears to offer no benefit [41].

A retrospective case–control study [4] sparked controversy concerning the use of short-acting calcium channel blockers in treating hypertension. The study involved 623 cases of fatal and non-fatal myocardial infarction over a period of 8 years, and 2032 age- and sex-matched controls. The risk of myocardial infarction in patients taking calcium channel blockers was 16 per 1000, compared with 10 per 1000 in patients taking beta-blockers or thiazides. However, this result may have been an example of confounding by indication, since patients exposed to calcium channel blockers will have been more likely to have had peripheral vascular disease, lung disease (a low forced expiratory volume being a risk factor for cardiovascular disease), higher serum cholesterol concentrations, and diabetes mellitus. Careful statistical analysis was carried out in an attempt to control for some of the confounding factors, but such confounding can only be properly controlled for in a randomized study. A meta-analysis of 16 randomized secondary prevention studies in patients with coronary heart disease showed that the use of short-acting nifedipine is associated with an increased mortality in a dose-related manner (dose, risk: 30–50 mg, 1.06; 60 mg, 1.18; 80 mg, 2.83) [5]. However, the event rates in this study were relatively small. A prospective cohort study in 906 elderly hypertensive patients showed that short-acting nifedipine is associated with a relative mortality risk of 1.7 compared with beta-blockers [42]. After the publication of these studies, the FDA recommended that short-acting nifedipine should no longer be used in hypertension or unstable angina [43].

Disturbances of cardiac rhythm

Calcium channel blockers differ in their effects on the myocardial conduction system. Both verapamil and diltiazem have significant inhibitory effects on both sinoatrial and atrioventricular nodal function, whereas nifedipine has little or no effect. Nevertheless, nifedipine can on occasion cause troublesome bradydysrhythmias [44,45].

Severe conduction disturbances can also occur if calcium channel blockers are used in hypertrophic cardiomyopathy [46], but these drugs are used in this condition [47].

Hypotension

There have been many case reports of symptomatic hypotension, usually in hypertensive patients treated with large dosages of calcium channel blockers [48,49] or in patients with myocardial infarction [50]. These may represent injudicious prescribing rather than true adverse drug effects. In the DAVIT II study, 1.9% of the verapamil-treated group versus 1.6% of the placebo-treated group developed hypotension or dizziness [40]; the frequency of hypotension in a randomized study of diltiazem after infarction was 0.6% in the drug-treated group and 0.2% in the placebo-treated group [37].

Respiratory

Adverse respiratory effects are uncommon with calcium channel blockers. However, three cases of acute bronchospasm accompanied by urticaria and pruritus have been reported in patients taking verapamil [51], and a patient with Duchenne-type muscular dystrophy developed respiratory failure during intravenous verapamil therapy for supraventricular tachycardia [52]. Recurrent exacerbations of asthma occurred in a 66-year-old lady with hypertension and bronchial asthma given modified-release verapamil [53].

In pulmonary hypertension, both verapamil and nifedipine increase mean right atrial pressure in association with hypotension, chest pain, dyspnea, and hypoxemia; the severe hemodynamic upset resulted in cardiac arrest in two patients after verapamil and death in another after nifedipine [54]. A patient with pulmonary hypertension also developed pulmonary edema whilst taking nifedipine [55] and another seems to have developed this as an allergic reaction [56].

Nervous system

Calcium channel blockers can cause parkinsonism. Of 32 patients with this complication, only three had made a full recovery 18 months after withdrawal; patients under 73 years of age tended to have a better prognosis [57]. It is not known if these patients would have developed parkinsonism in any case, and whether the drugs merely act as precipitants.

Calcium channel blockers can worsen myasthenic syndromes. Myasthenia gravis can deteriorate with oral verapamil [58]. A patient with Lambert–Eaton syndrome and a small-cell carcinoma of the lung developed respiratory failure within hours of starting treatment with verapamil for atrial flutter, and required assisted ventilation [59]. Only after verapamil had been withdrawn did breathing improve. Verapamil affects calcium channels in nerve membranes in animals, but the experimental concentrations used exceeded those found in clinical practice [59].

Thus, the evidence for a drug-related effect is circumstantial. In another case, diltiazem triggered Lambert–Eaton syndrome, which improved with drug withdrawal [60].

Sensory systems

Eyes

Painful eyes occurred in 14% of patients taking nifedipine compared with 9% in captopril-treated patients in a post-marketing surveillance study [61]. The mechanism is unknown but is not via ocular vasodilatation [62].

Taste

Transient disturbances of taste and smell, without other signs of neurological deficit, have been reported after nifedipine and diltiazem. The time to the onset of symptoms after nifedipine varied from days to months, and symptoms regressed within 24 hours of withdrawal [63]. With diltiazem the effect gradually abated over 10 weeks, despite continuation of therapy [64].

Psychiatric

A patient taking diltiazem developed the signs and symptoms of mania [65] and another developed mania with psychotic features [66]. There have also been reports that nifedipine can cause agitation, tremor, belligerence, and depression [67], and that verapamil can cause toxic delirium [68]. Nightmares and visual hallucinations have been associated with nifedipine [69]. Depression has been reported as a possible adverse effect of nifedipine [70].

Some reports have suggested that calcium channel blockers may be associated with an increased incidence of depression or suicide. However, there is a paucity of evidence from large-scale studies. A study of the rates of depression with calcium channel blockers, using data from prescription event monitoring, involved gathering information on symptoms or events in large cohorts of patients after the prescription of lisinopril, enalapril, nicardipine, and diltiazem by general practitioners [71]. The crude overall rates of depression during treatment were 1.89, 1.92, and 1.62 per 1000 patient-months for the ACE inhibitors, diltiazem, and nicardipine respectively. Using the ACE inhibitors as the reference group, the rate ratios for depression were 1.07 (95% CI = 0.82, 1.40) and 0.86 (0.69, 1.08) for diltiazem and nicardipine respectively. This study does not support the hypothesis that calcium channel blockers are associated with depression.

Endocrine

In six hypertensive patients given nitrendipine 20 mg/day for 30 days, there was inhibition of aldosterone response but no significant change in ACTH secretion in response to corticotrophin-releasing hormone [72].

The calcium-dependent pathway of aldosterone synthesis in the zona glomerulosa is blocked by calcium channel blockers, producing a negative feedback increase in the pituitary secretion of ACTH, which in turn causes hyperplasia of the zona glomerulosa. This leads to increased production of androgenic steroid intermediate products and subsequently testosterone, which acts on gingival cells and matrix, giving rise to gingival hyperplasia (see the section on **Mouth and teeth**).

Metabolism

Calcium transport is essential for insulin secretion, which is therefore inhibited by calcium channel blockers [73]. Despite this, calcium channel blockers generally have minimal effects on glucose tolerance in both healthy and diabetic subjects. Oral glucose tolerance is not affected by verapamil, and basal blood glucose concentrations were not altered during long-term verapamil administration [74]. Similarly, neither nifedipine nor nicardipine produced significant hyperglycemic effects in either diabetic or non-diabetic patients [75–77]. In 117 hypertensive patients nifedipine caused a significant rise in mean random blood glucose of only 0.3 mmol/l [78], an effect that was clearly of no clinical relevance. In the Treatment of Mild Hypertension Study, 4 years of monotherapy with amlodipine maleate caused no change compared with placebo in the serum glucose of 114 hypertensive patients [79]. In a review [80] it was concluded that in usual dosages calcium channel blockers do not alter glucose handling. However, in a few patients diabetes appeared de novo or worsened considerably on starting nifedipine [78,81], so there may be a small risk in some individuals.

Fluid balance

Edema of the legs is a well-recognized reaction to nifedipine and also occurs with verapamil, diltiazem, and the long-acting dihydropyridines [82,83], suggesting that this is a class effect of calcium channel blockers.

Hematologic

Calcium channel blockers rarely cause hematological effects. A hemorrhagic diathesis, including impaired platelet function, develops in chronic renal insufficiency, in which calcium channel blockers are used widely as antihypertensive agents. In 156 patients with moderate to severe chronic renal insufficiency not on hemodialysis calcium channel blockers prolonged the bleeding time (OR = 3.52; 95% CI = 1.01, 12.3) [84]. However, despite this effect, there were no clinically serious hemorrhagic events during the study. Among those taking calcium channel blockers, 21 patients with prolonged bleeding times were randomly assigned to two groups; in one group treatment was withdrawn and bleeding time shortened; in those who continued to take the treatment the bleeding time was unchanged.

Nifedipine has been reported to cause agranulocytosis [85] and leukopenia was attributed to diltiazem; the latter patient had scleroderma, active rheumatoid disease, and pulmonary fibrosis, but the white cell count fell after 3 weeks of diltiazem, recovered on withdrawal, and fell on rechallenge [86]. Diltiazem has also been reported to cause immune thrombocytopenia in a 68-year-old man with angina [87].

Mouth and teeth

Gingival hyperplasia, similar to that seen with phenytoin and ciclosporin, is a rare but well-recognized adverse effect of nifedipine [88]. It has also been reported in patients taking felodipine [89,90], nitrendipine [91], and verapamil [92], suggesting that this adverse effect is a class effect. Only one case of gingival hyperplasia related to calcium channel blockers was reported to the Norwegian Adverse Drug Reaction Committee up to 1991, despite their widespread use [93]. However, subclinical gingival hyperplasia on tissue histology was found in 83% and 74% of patients taking nifedipine and diltiazem respectively [94]. The reaction generally occurs within a few months of starting treatment, and in some cases drug withdrawal produces marked regression of clinical hyperplasia. The mechanism of this adverse effect is unclear, but has been proposed to involve a hormonal imbalance in the hypothalamic–pituitary–adrenal axis [95].

Periodontal disease has been assessed in 911 patients taking calcium channel blockers, of whom 442 were taking nifedipine, 181 amlodipine, and 186 diltiazem, and in 102 control subjects [96]. There was significant gingival overgrowth in 6.3% of the subjects taking nifedipine, while the prevalence induced by amlodipine or diltiazem was not significantly different than in the controls. The severity of overgrowth in the nifedipine group was related to the amount of gingival inflammation and also to sex, men being three times as likely to develop overgrowth than women.

Gastrointestinal

Because of effects on smooth muscle, the calcium channel blockers (particularly verapamil [97] but also diltiazem) can cause constipation. This may be due to colonic motor activity inhibition [98]. Gastroesophageal reflux can also occur, and the calcium channel blockers should be avoided in patients with symptoms suggestive of reflux esophagitis [99]. Calcium channel blockers (verapamil, diltiazem, and nifedipine) can also be associated with an increased incidence of gastrointestinal bleeding, as reported in a prospective cohort study in 1636 older hypertensives, with a relative risk of 1.86 (95% CI = 1.22, 2.82) compared with beta-blockers [7]. However, this finding was not confirmed in other retrospective studies [13,100,101].

Liver

Mild hepatic reactions have been observed in association with verapamil, nifedipine [102–105], and diltiazem [106,107]. In some cases fever, chills, and sweating have been associated with right upper quadrant pain, hepatomegaly, and mild increases in serum bilirubin and transaminase activity; in others, patients have remained asymptomatic. One patient had granulomatous hepatitis with diltiazem [108]; another had a periportal infiltrate rich in eosinophils while taking verapamil [109]. The increase in liver enzyme activities is generally transient, although mild persistent abnormalities have been seen. Occasionally, extreme increases in hepatic enzyme activities have been reported [85,106]. Their frequency appears to be low, and since the symptoms and signs are mild they could easily be overlooked.

Skin

Apart from minor flushing and leg erythema associated with edema, skin reactions with calcium channel blockers are infrequent; the frequency has been estimated at 1.3% for diltiazem [110].

An erythematous rash with painful edema has been described with nifedipine [111] and also with diltiazem, but without the edematous element [109].

Mild erythema multiforme and Stevens–Johnson syndrome have been reported as probable reactions to diltiazem [85] and long-acting nifedipine [112].

Nifedipine, verapamil, and diltiazem have all been implicated as possible causes of erythema multiforme and its variants, Stevens–Johnson syndrome and toxic epidermal necrolysis, and/or exfoliative dermatitis from FDA data [113].

Psoriasiform eruptions have been reported in patients taking verapamil and nicardipine [114].

Photo-induced annular or papulosquamous eruptions due to subacute cutaneous lupus erythematosus with positive antinuclear, anti-Ro, and anti-La antibodies have been reported with verapamil, nifedipine, and diltiazem [115]. The association of calcium channel blockers with photo-damage has been assessed in 82 patients with renal transplants [116]. Most of the patients (90%) had photo-damaged skin (50% mild, 24% moderate, and 13% severe) and 53 (65%) had used a calcium channel blocker (49 nifedipine and four amlodipine). There were strong associations between calcium channel blockers and the grade of photo-damage and the presence of telangiectasia, with a less marked association with solar elastosis. There was no convincing association between the grade of photo-damage and the duration of treatment.

Reproductive system

Calcium channel blockers can occasionally cause menorrhagia [117] and gynecomastia [118].

Immunologic

Verapamil, nifedipine, and diltiazem have all been associated with allergic reactions, including skin eruptions and effects on liver and kidney function. Nifedipine has also been reported to cause a febrile reaction [119], and diltiazem was associated with fever, lymphadenopathy, hepatosplenomegaly, an erythematous maculopapular rash, and eosinophilia in a 50-year-old man [120].

LONG-TERM EFFECTS

Drug withdrawal

The possibility of a calcium antagonist withdrawal syndrome has been raised [121–130], as it has been reported that withdrawal of verapamil, nifedipine, and diltiazem can worsen

angina or even cause myocardial infarction. However, in a randomized, double-blind study of withdrawal of nifedipine in 81 patients before coronary artery bypass surgery, angina at rest occurred only in patients who had experienced similar symptoms previously, and there were no early untoward effects of drug withdrawal [123]. If a withdrawal syndrome does exist, it could be due to rebound coronary vasospasm, but the present weight of evidence suggests that withdrawal results in no more than the loss of a useful therapeutic effect or the unmasking of progressive disease [130].

Tumorigenicity

A retrospective cohort study in 5052 elderly subjects, of whom 451 were taking verapamil, diltiazem, or nifedipine, showed that these drugs were associated with a cancer risk of 1.72 (95% CI = 1.27, 2.34), and there was a significant dose–response relation [8]. A small risk of cancer (RR = 1.27; 95% CI = 0.98, 1.63) with calcium channel blockers was reported in a nested case–control retrospective study involving 446 cases of cancers in hypertensive patients [131]. However, the authors concluded that this finding may have been spurious, as there was no relation between the cancer risk and the duration of drug use. Another study did not show any excess cancer risk with short-acting nifedipine after myocardial infarction in patients followed up for 10 years, although there were only 22 cancer deaths in 2607 patients [132]. Neither did the much larger Bezafibrate Infarction Prevention (BIP) Study, which reported cancer incidence data in 11 575 patients followed for a mean period of 5.2 years, with 246 incident cancer cases, 129 among users (2.3%) and 117 (2.1%) among non-users of calcium channel blockers [133]. Others also failed to find a positive link between calcium channel blockers and cancer [14,134]. However, elderly women taking estrogens and short-acting calcium channel blockers had a significantly increased risk of breast carcinoma (hazard ratio = 8.48; 95% CI = 2.99, 24) [135].

In another study, the responses of 975 women with invasive breast carcinoma were compared with the responses of 1007 women in a control group [136]. Women who had ever used calcium channel blockers, beta-blockers, or ACE-inhibitors did not have an altered risk of breast carcinoma compared with women who had never used antihypertensive drugs. There was a modestly increased risk of breast carcinoma among users of immediate-release calcium channel blockers (OR = 1.5; 95% CI = 1.0, 2.1), thiazide diuretics (OR = 1.4; 95% CI = 1.1, 1.8), and potassium-sparing diuretics (OR = 1.6; 95% CI = 1.2, 2.1). No clear trends emerged from the analysis of the correlations between risk and duration of use. This controversy can perhaps only be resolved by prospective studies with longer follow-up periods [137], although ideal studies are unlikely ever to be conducted.

SECOND-GENERATION EFFECTS

Pregnancy

The calcium channel blockers have had very limited use in pregnancy. The absence of reports of fetal deaths, malformations, or other maternal or neonatal adverse effects cannot therefore be construed as indicating safety. However, a comparison of nifedipine and hydralazine in 54 patients with severe pre-eclampsia showed that nifedipine is more effective, allowing delivery of more mature infants [138].

- Modified-release nifedipine 40 mg tds caused marked hypotension when used to delay preterm labor in a previously healthy 29-year-old woman who started contracting at 29 weeks; the hypotension may have precipitated an uncomplicated non-Q-wave myocardial infarction [139].

When nifedipine is combined with intravenous magnesium to delay preterm labor, colonic pseudo-obstruction can occur [140].

Lactation

Both verapamil [141] and diltiazem [142] are excreted in breast milk, but the risk to the suckling infant is unclear.

SUSCEPTIBILITY FACTORS

Patients with impaired function of the sinus node or impaired atrioventricular conduction can develop sinus bradycardia, sinus arrest, heart block, hypotension and shock, and even asystole, with verapamil [143] or diltiazem. These drugs should not be given to patients with aberrant conduction pathways associated with broad-complex tachydysrhythmias, and they can cause severe conduction disturbances in hypertrophic cardiomyopathy.

Similarly, verapamil should be used with caution in patients with heart failure, and both diltiazem and nifedipine can cause problems in patients with poor cardiac reserve. However, the PRAISE study [18] suggested that amlodipine may be used safely, even in the presence of severe heart failure optimally treated with diuretics, digoxin, and ACE inhibitors. In this study, amlodipine significantly reduced cardiac mortality by more than a third in non-ischemic dilated cardiomyopathy, without significantly affecting mortality in ischemic cardiomyopathy [144].

Calcium channel blockers should be avoided when possible in the peri-infarction period.

The use of calcium channel blockers in patients with pulmonary hypertension has been associated with cardiac arrest and sudden death.

Caution should be exercised in using verapamil in patients with hepatic cirrhosis, as its metabolism is reduced, leading to high plasma concentrations and potential toxicity [145]. Similarly, lower starting and maintenance doses of other calcium channel blockers should be used in the presence of liver impairment. This also applies to patients with chronic renal insufficiency, especially those taking the modified-release formulation of verapamil [146].

DRUG ADMINISTRATION

Drug overdose

The treatment of overdosage with calcium channel blockers has been reviewed [147,148]; other reports have

reviewed poisoning with verapamil [149–151], and other calcium channel blockers [152,153].

The features appear to be arterial hypotension, bradycardia due to sinus node depression and atrioventricular block, and congestive cardiac failure and angina [154–156]. Although the therapeutic effects are different according to the drug, in overdosage the effects are similar [152]. Severe metabolic acidosis (usually lactic acidosis) and generalized convulsions can also occur [157] and hypoglycemia has been reported [158]. Non-cardiogenic pulmonary edema has been reported with diltiazem [159] and verapamil [160]. Several deaths have occurred with verapamil.

- An overdose of nifedipine 280 mg produced marked vasodilatation in a young patient with advanced renal insufficiency; it was successfully treated with intravenous calcium [161].

An overdose of a mixture of calcium channel blockers mimicked acute myocardial infarction [162].

- A 42-year-old man developed shortness of breath, weakness, sweating, and left bundle branch block. Coronary angiography showed only non-obstructive lesions, ruling out acute closure of a coronary artery, and his left ventriculogram showed no wall motion abnormalities, but rather a markedly hyperdynamic left ventricle with an ejection fraction of 80%. Despite this, he subsequently developed profound bradycardia and hypotension, which were refractory to standard treatments, including pressor agents, calcium, and transvenous pacing. He gradually improved over several days and made a full recovery. After extubation he admitted to having taken "several" tablets each of long-acting verapamil, diltiazem, and nifedipine, of unclear dosages, and over an unclear period time, trying to self-medicate for symptoms he related to life-long paroxysmal supraventricular tachycardia.

This case highlights the fact that calcium channel blocker overdose must be considered in the differential diagnosis of patients who present with apparent acute myocardial infarction.

Treatment consists of gastric lavage, activated charcoal, and cathartics. Contrary to popular belief, significant overdosage of immediate-release verapamil can be associated with delayed absorption, as suggested by a case report, the authors of which suggested the use of repeated doses of activated charcoal [149]. In severe cases total gut lavage should be considered. Intravenous calcium gluconate [163], glucagon [164], pressor amines (isoprenaline, adrenaline, or dobutamine), artificial ventilation, and cardiac pacing may all be required. Hemoperfusion does not appear to influence the clinical course, but 4-aminopyridine reversed the features of a modest accidental overdose of verapamil in a patient on maintenance hemodialysis [165]. The rationale for the use of aminopyridine, an antagonist of non-depolarizing neuromuscular blocking agents, supported by prior animal experiments, was the enhancement of transmembrane calcium flux and the facilitation of synaptic transmission. This is of potential value, in view of the apparent unresponsiveness of some patients to supportive measures.

Five cases of overdose of calcium channel blockers have been reported [166]:

- a 34-year-old woman who took amlodipine 0.86 mg/kg;
- a 48-year-old man who took an unknown amount of modified-release diltiazem;
- a 5-month-old girl inadvertently given nifedipine 20 mg;
- a 14-year-old girl who took modified-release verapamil 30 mg/kg;
- a 31-year-old man who took modified-release verapamil 71 mg/kg.

All were successfully treated with hyperinsulinemia/euglycemia therapy. The authors described the mechanism of action of this form of therapy, which is mainly related to improvement in cardiac contractility and peripheral vascular resistance and reversal of acidosis. They proposed indications and dosing for this therapy consisting in most cases of intravenous glucose with an intravenous bolus dose of insulin 1 U/kg followed by an infusion of 0.5–1 U/kg/hour until the systolic blood pressure is over 100 mm/Hg and the heart rate over 50/minute. Hyperinsu linemia/euglycemia therapy is currently reserved as an adjunct to conventional therapy and is recommended only after an inadequate response to fluid resuscitation, high-dose calcium salts, and pressor agents.

- A 43-year old man took amlodipine 560 mg and failed to respond to fluid resuscitation, calcium salts, glucagon, and noradrenaline/adrenaline inotropic support [167]. However, intravenous metaraminol 2 mg followed by 83 micrograms/minute produced an improvement in his blood pressure, cardiac output, and urine output.
- A 65-year-old man with aortic stenosis died after mistakenly taking six tablets of modified-release diltiazem SR 360 mg [168]. He developed symptoms of toxicity within 7 hours and died after 17 hours. The diltiazem concentration in an antemortem blood sample 11.5 hours after ingestion was 2.9 μg/ml and in a postmortem sample of central blood 6 μg/ml.

DRUG–DRUG INTERACTIONS

See also Mibefradil; Midazolam; Phosphodiesterase type V inhibitors; Rifamycins; Theophylline and related compounds.

Combinations of calcium channel blockers

Paralytic ileus has been attributed to the combined use of diltiazem and nifedipine [169].

- A 62-year-old man with chest pain underwent cardiac catheterization. The diagnosis was vasospastic angina and he was given nifedipine 20 mg bd; when his angina attacks persisted he was also given oral diltiazem 100 mg bd. After 2 days, although his angina was well controlled, abdominal distension and vomiting occurred, and an X-ray suggested intestinal ileus. The drugs were withdrawn and the ileus resolved. It recurred when the treatment was resumed and gradually resolved again after withdrawal.

The disorder was suspected to be due to enhanced pharmacodynamic effects caused by the combination of the two calcium channel blockers. However, plasma concentrations of nifedipine have also been reported to increase about three-fold when it is combined with diltiazem [170].

In a Prescription-Event Monitoring study in 3085 patients, mean age 65 years, one patient developed collapse and severe bradycardia after starting to take a dihydropyridine calcium channel blocker within 24 hours of stopping mibefradil [171].

Azaspirones and benzodiazepines

Diltiazem and verapamil compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone [172–174].

Beta-adrenoceptor antagonists

The greatest potential for serious mishap arises from interactions between calcium channel blockers (especially verapamil and related compounds) and beta-adrenoceptor antagonists [175,176]. This combination can cause severe hypotension and cardiac failure, particularly in patients with poor myocardial function [177–179]. The major risk appears to be associated with the intravenous administration of verapamil to patients who are already taking a beta-blocker [180], but a drug-like tiapamil, which closely resembles verapamil in its pharmacological profile, might be expected to carry a similar risk [181]. Conversely, intravenous diltiazem does not produce deleterious hemodynamic effects in patients taking long-term propranolol [182]. However, there have been instances when the combination of diltiazem with metoprolol caused sinus arrest and atrioventricular block [183].

The concurrent use of oral calcium channel blockers and beta-adrenoceptor antagonists in the management of angina pectoris or hypertension is less likely to result in heart block or other serious adverse effects [184], and these two drug groups are commonly used together. However, caution is still advised, and nifedipine or other dihydropyridine derivatives would be preferred in this type of combination [26,185,186]. Nevertheless, the combination of nifedipine with atenolol in patients with stable intermittent claudication resulted in a reduction in walking distance and skin temperature, whereas either drug alone produced benefits [187].

Bupivacaine

Calcium channel blockers in combination with bupivacaine produce significant negative inotropic effects on the heart in animals, possibly due to reduced protein binding of the local anesthetic, as well as a generalized myocardial depressant effect [188,189].

However, bupivacaine cardiotoxicity was reduced in rats by pretreatment with low doses of calcium channel blockers [190]. In vivo, the LD50 for bupivacaine was increased from 3.08 to 3.58 mg/kg after pretreatment with verapamil 150 micrograms/kg, and to 3.50 mg/kg after nimodipine 200 micrograms/kg. Of the rats that died, only one developed cardiac arrest first, whilst the majority developed respiratory arrest. In vitro, bupivacaine alone dose-dependently reduced heart rate, contractile force, and coronary perfusion pressure. Dysrhythmias were also noted: bradycardias, ventricular extra beats, and ventricular tachycardia were the most common. Verapamil made no difference to these adverse effects, but nimodipine significantly reduced the negative chronotropic and dysrhythmogenic effects of bupivacaine. These results, although interesting, cannot be used to reach any clinical conclusions, particularly as the mechanism of interaction between bupivacaine and calcium channel blockers has yet to be elucidated.

Buspirone

In a randomized placebo-controlled trial, the possible interactions of buspirone with verapamil and diltiazem were investigated. Both verapamil and diltiazem considerably increased plasma buspirone concentrations, probably by inhibiting CYP3A4. Thus, enhanced effects and adverse effects of buspirone are possible when it is used with verapamil, diltiazem, or other inhibitors of CYP3A4 [191].

Carbamazepine

A pharmacokinetic interaction has been described between carbamazepine and the calcium channel blockers verapamil [192] and diltiazem [193]. With both drugs, inhibition of the hepatic metabolism of carbamazepine resulted in increased serum carbamazepine concentrations and neurotoxicity, with dizziness, nausea, ataxia, and diplopia. Adding nifedipine to carbamazepine was not associated with alterations in steady-state carbamazepine concentrations [193].

Cardiac glycosides

Calcium channel blockers have varying effects on the disposition of digoxin. The calcium channel blockers for which varying amounts of information are available include cinnarizine, diltiazem, felodipine, fendiline, gallopamil, isradipine, lidoflazine, mibefradil, nicardipine, nifedipine, nitrendipine, tiapamil, and verapamil [194].

The main mechanism is inhibition of digoxin renal tubular secretion by inhibition of P glycoprotein. In a review of the interactions of calcium channel blockers with digoxin, in which their clinical relevance was assessed, it was concluded that serious consequences can be prevented by careful monitoring, especially in patients whose serum digoxin concentration is already near the upper end of the therapeutic range [195].

Bepridil

An interaction of digoxin with bepridil has been described [196].

Diltiazem

Studies of the effects of diltiazem on the pharmacokinetics of digoxin have yielded variable results. In some studies diltiazem 120–240 mg/day increased steady-state plasma digoxin concentrations by about 20–40% [197–200], although not in other studies [201]. In some studies it reduced the total body clearance of digoxin, with changes in both renal and non-renal clearances [202], although others did not find this [203]. In at least one case digoxin toxicity was attributed to this interaction [204]. In eight patients with chronic heart failure taking digoxin 0.25 mg/day, diltiazem 180 mg/day increased the AUC and mean steady-state serum concentrations of digoxin by 50% and reduced its total clearance [205].

In one study, diltiazem reduced the steady-state total body clearance of beta-acetyldigoxin in 12 healthy men, perhaps because of reduced renal and non-renal clearances [202].

Mibefradil

In 40 healthy subjects mibefradil 50 or 100 mg/day for 6 days had no significant effects on the steady-state pharmacokinetics of digoxin, apart from a very small increase in the C_{max} [206].

Nifedipine

The interaction of digoxin with nifedipine increases plasma digoxin concentrations by only about 15% [207,208] and is less important. In one study it had no effect [199].

Nitrendipine

An interaction of digoxin with nitrendipine has been described [209].

Tiapamil

Tiapamil reversed digoxin-induced splanchnic vasoconstriction in healthy men [210], but this has no direct effect on systemic hemodynamics.

Verapamil

Verapamil increases plasma digoxin concentrations at steady state by inhibiting the active tubular secretion and non-renal clearance of digoxin [199,211,212]. It suppresses renal digoxin elimination acutely, but this suppression disappears over a few weeks [213]. However, inhibition of the extrarenal clearance of digoxin persists, and the result of this complex interaction is an increase in steady-state plasma digoxin concentrations of less than 100%. There is anecdotal evidence that this can result in digitalis toxicity [212,214]. However, the pharmacodynamic effects of digoxin are apparently reduced by verapamil [215], so that dosage adjustment may be unnecessary. Patients taking both drugs should be carefully monitored.

Cardiovascular collapse and/or asystole has followed the use of intravenous verapamil in patients taking oral digoxin alone [216] or in combination with quinidine, propranolol, or disopyramide [181]. Verapamil reversed digoxin-induced splanchnic vasoconstriction in healthy men [210], but this has no direct effect on systemic hemodynamics.

Ciclosporin

Calcium channel blockers are given to transplant patients for their protective effect against ciclosporin-induced nephrotoxicity and to optimize ciclosporin immunosuppression in order to reduce early rejection of renal grafts. Nifedipine has been used to treat ciclosporin-induced hypertension, although amlodipine may be just as effective [217].

However, some calcium channel blockers have pharmacokinetic interactions: diltiazem, verapamil, nicardipine, and amlodipine increase ciclosporin concentrations, whereas nifedipine, felodipine, and isradipine do not [218–222]. Two confirmations of these observations have been published. In a retrospective study of 103 transplant patients verapamil and diltiazem, but not nifedipine or isradipine, caused a significant increase in plasma ciclosporin concentrations [223]. The effect of verapamil and diltiazem on ciclosporin concentrations was independent of dosage. In a crossover comparison between verapamil, felodipine, and isradipine in 22 renal transplant recipients, verapamil interacted pharmacokinetically with ciclosporin but felodipine and isradipine did not [224].

Nine kidney transplant recipients had an increase in trough whole blood ciclosporin concentrations of 24–341% after introduction of nicardipine [225]. A similar interaction has been reported with diltiazem [226] and verapamil [227].

A large amount of data has accumulated on the effects of various calcium channel blockers on ciclosporin metabolism or a possible renal protective effect. Diltiazem, nicardipine, or verapamil inhibit ciclosporin metabolism, and this has been investigated as a potential beneficial combination for ciclosporin-sparing effects, particularly for diltiazem or verapamil [218,228]. Any change in the formulation of calcium channel blockers in patients previously stabilized should be undertaken cautiously because unpredictable changes in ciclosporin concentrations can occur [229]. In contrast, nifedipine, isradipine, or felodipine do not significantly affect ciclosporin pharmacokinetics [218,222]. Results obtained with amlodipine are conflicting; some studies have shown no effect, while others indicate an increase of up to 40% in ciclosporin blood concentrations [230]. Co-administration of calcium channel blockers is also regarded as a valuable option in the treatment of ciclosporin-induced hypertension, or to prevent ciclosporin nephrotoxicity.

There are conflicting results from studies on the protective role of calcium channel blockers in patients taking ciclosporin in regard to blood pressure and preservation of renal graft function. In a multicenter, randomized, placebo-controlled study in 131 de novo recipients of cadaveric renal allografts, lacidipine improved graft function from 1 year onwards, but had no effect on acute rejection rate, trough blood ciclosporin concentrations, blood pressure, number of antihypertensive drugs, hospitalization rate, or rate of adverse events [231].

The combination of ciclosporin with nifedipine produces an additive on gingival hyperplasia, with an increased prevalence and/or severity in both children [232,233] and adults [234–236]. In contrast, verapamil had no significant additional effects on the prevalence or severity of ciclosporin-induced gingival overgrowth [237].

Cimetidine

The histamine H_2 receptor antagonist cimetidine increases plasma concentrations of nifedipine and delays its elimination by inhibition of hepatic mono-oxygenases. Maximum

plasma nifedipine concentrations and AUC can be increased by as much as 80%, and this results in a significant increase in the antihypertensive and antianginal effects of nifedipine and also toxicity [238,239].

Cimetidine also increases plasma concentrations of nitrendipine and nisoldipine [209,240].

Ranitidine, which inhibits the microsomal monooxygenase system only slightly, does not alter plasma dihydropyridine concentrations to the same extent [241].

Corticosteroids—glucocorticoids

Methylprednisolone concentrations increased with the co-administration of diltiazem (2.6-fold) and mibefradil (3.8-fold) [242].

Dantrolene

Dantrolene interacts with verapamil and with diltiazem, causing myocardial depression and cardiogenic shock [243].

The combination of dantrolene with calcium channel blockers, such as verapamil, can result in severe cardiovascular depression and hyperkalemia [244,245], so that extreme care is required.

Fluconazole

Fluconazole has been reported to increase nifedipine concentrations.

- Fluconazole enhanced the blood pressure-lowering effects of nifedipine by increasing its plasma concentrations in a 16-year-old patient with malignant pheochromocytoma taking chronic nifedipine for arterial hypertension who was given fluconazole for *Candida* septicemia [246].

Ketoconazole

The effects of ketoconazole 200 mg on the pharmacokinetics of nisoldipine 5 mg have been investigated in a randomized, cross-over trial [247]. Pretreatment with and concomitant administration of ketoconazole resulted in 24-fold and 11-fold increases in the AUC and C_{max} of nisoldipine, respectively. The ketoconazole-induced increase in plasma concentrations of the metabolite M9 was of similar magnitude. Thus, ketoconazole and other potent inhibitors of CYP3A should not be used concomitantly with nisoldipine.

In an intestinal perfusion study of the effect of ketoconazole 40 μg/ml on the jejunal permeability and first-pass metabolism of (*R*)- and (*S*)-verapamil 120 μg/ml in six healthy volunteers, ketoconazole did not alter the jejunal permeability of the isomers, suggesting that it had no effect on the P-glycoprotein mediated efflux. However, the rate of absorption increased, suggesting inhibition by ketoconazole of the gut wall metabolism of (*R*/*S*)-verapamil by CYP3A4 [248].

Lithium

Lithium clearance is reduced by about 30% by nifedipine [249].

- A 30-year-old man required a reduction in lithium dosage from 1500 to 900 mg/day to maintain his serum lithium concentration in the target range shortly after he started to take nifedipine 60 mg/day [250].

There have been reports of neurotoxicity, bradycardia, and reduced lithium concentrations associated with verapamil [251–253].

Prazosin

An interaction of prazosin with nifedipine or verapamil resulted in acute hypotension [254,255]. The mechanism appears to be partly kinetic (the systemic availability of prazosin increasing by 60%) and partly dynamic.

Sildenafil

Retrospective analysis of clinical trials has suggested that the concomitant use of antihypertensive drugs did not lead to an increase in adverse events in patients also taking sildenafil [256].

Hypertensive patients taking amlodipine, in contrast to glyceryl trinitrate, had only a minor supplementary fall in blood pressure when challenged with a single dose of sildenafil, and a few had a mild to moderate headache [257].

Diltiazem is metabolized by CYP3A4 and was held responsible for unanticipated prolonged hypotension after sublingual glyceryl trinitrate in a patient who underwent coronary angiography 2 days after last using sildenafil [258].

Simvastatin

In a meta-analysis of megatrials of simvastatin, the overall incidence of myopathy was 0.025%; the same proportion of those with myositis had used calcium channel blockers as the proportion overall, suggesting that there is no important interaction between these two groups of drugs [259].

However, diltiazem interacts with lovastatin although not with pravastatin [260], and an interaction has also been observed with simvastatin in a 75-year-old man who developed impaired renal function [261]. He had extreme weakness and muscle pain.

Tacrolimus

A 3-day course of diltiazem 90 mg/day produced a four-fold increase in tacrolimus trough concentrations in a 68-year-old patient with a liver transplant [262].

In a non-randomized, pharmacokinetic study, four patients taking tacrolimus after kidney and liver transplantation were given diltiazem in seven incremental dosages of 0–180 mg at 2-week intervals [263]. The mean tacrolimus-sparing effect was similar to the ciclosporin-sparing effect previously reported. This effect occurred at a lower dose of diltiazem in renal transplant patients than in liver transplant patients. Tacrolimus is

metabolized by CYP3A4 and is also a substrate for P glycoprotein, and this interaction could have occurred by inhibition of these mechanisms.

A retrospective study has shown a significant improvement in kidney function and a 38% reduction in tacrolimus dosage requirements in patients taking both nifedipine and tacrolimus compared to patients not taking nifedipine [264].

Theophylline

Theophylline toxicity has been reported in several patients, apparently stabilized on theophylline, after the introduction of verapamil [265] or nifedipine [266].

Tubocurarine

Calcium channel blockers, such as verapamil and nifedipine, can potentiate neuromuscular blocking agents [267,268] and it has been suggested that in long-term use they can accumulate in muscle and make block-reversal difficult [269].

FOOD–DRUG INTERACTIONS

Grapefruit juice

The ability of grapefruit to increase the plasma concentrations of some drugs was accidentally discovered when grapefruit juice was used as a blinding agent in a drug interaction study of felodipine and alcohol [270]. It was noticed that plasma concentrations of felodipine were much higher when the drug was taken with grapefruit juice than those previously reported for the dose of drug administered. In other studies concurrent administration of grapefruit juice and felodipine increased the AUC, causing increased heart rate, and reduced diastolic blood pressure [271], or caused increased blood pressure and heart rate, headaches, flushing, and light-headedness [272]. Grapefruit increases plasma concentrations of nifedipine [273] and nisoldipine [274] by increasing their systemic availability [275]; with nisoldipine or nitrendipine there was an increase in heart rate.

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