Calcium channel blockers: indications and limitations

1. Clinical pharmacology and use as antiarrhythmic agents

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In the atmosphere of euphoria that often surrounds introduction of new drugs, indications may be exaggerated and limitations downplayed. This two-part article carefully assesses the advantages and disadvantages of the new calcium channel blocking drugs in the various indications for which their use has been approved and looks into possible future applications. Part 2, on use of these drugs in angina and other cardiac disorders, begins on page 115.

Clinical experience with the calcium channel blockers, or calcium ion antagonists, has been extensive around the globe, and these pharmacologic agents are now being introduced in the United States. Nevertheless, even at this writing, critical evaluation of these drugs continues, and well-controlled studies are being completed. We expect these drugs to be widely used in this country in the near future for various cardiovascular disorders.

Calcium and cardiovascular function

The predominant action of the calcium channel blockers is to oppose calcium at specific cellular sites, such as membranes. Since calcium is a critically important ion in cardiovascular function, the impeding of calcium has numerous effects.

Calcium plays a major role in linking the electrical depolarization of a cell to contraction. This process, excitation-contraction coupling, is triggered by a small amount of calcium that enters the cell during the plateau phase of the action potential (phase 2). The contractile proteins, actin and myosin, interact when the regulatory proteins, troponin and tropomyosin, interact; the initial stimulus appears to be calcium.

Calcium also plays an important role in cardiac electrical activity. The electrical activity of the sinus and atrioventricular (AV) nodal cells is especially dependent on the "slow current" carried by calcium, whereas the rest of the specialized conduction system is more dependent on a brief, intense, inward "fast current" carried by sodium. The sodium channel is less important in the sinus and AV nodal cells.

In addition, calcium is instrumental in ischemic cells, especially in the presence of high catecholamine concentrations, increased extracellular potassium, excessive myocardial stretch, or a variety of other ischemia-related conditions. Smooth muscle tone in coronary arteries is critically influenced by alterations in the influx of calcium, and the peripheral vasculature is similarly affected.

Calcium is critical to many other metabolic functions in cardiac cells. Catecholamines achieve their intracellular actions by influencing calcium, and many intracellular metabolic pathways depend on calcium. Uncontrolled influx of calcium may be one of the early cellular events that commit ischemic cells to death.

There are also endocrine functions that are critically related to transmembrane calcium ion influx. Such events as release of growth hormone, thyroid-stimulating hormone, and corticotropin have been shown in experimental models to be influenced by calcium channel blockers.[1]*

The calcium channel blockers act on superficially located membrane storage sites for calcium.[2] These pharmacologic agents do not act on calcium uptake, binding, or exchange by cardiac microsomes, nor do they affect calcium-activated adenosine triphosphatase.[3] In summary, then, the calcium

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The calcium channel blocking agents are heterogeneous in chemical structure and action.

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channel blockers, which interfere with calcium action, affect various cardiovascular functions, including electrical activity, contractility, coronary and peripheral vascular tone, and metabolic functions, especially important during ischemia.

Drugs in the class
This review of calcium channel blockers concentrates on verapamil (Calan, Isoptin), nifedipine (Procardia), and diltiazem (Anginyl) because the widest clinical and experimental experience has been gained with these drugs. Additional calcium

channel blockers in various stages of investigation include methoxyverapamil, prenylamine, fendiline, perhexiline maleate (Pexid), lidoflazine, cinepazet maleate (Vascoril), and tiapamil.[4]

It is not correct to consider these drugs, as a class, completely specific competitive calcium channel blockers. They are heterogeneous in chemical structure and action, and in some experimental circumstances, their effects are not competitively reversed by increasing calcium. In addition, optimal isomers may possess various potencies, and the drugs have varied activity against specific calcium-dependent physiologic functions. In some circumstances, the drugs may not be affecting the calcium channel specifically, since in laboratory experiments they may influence the slow channel of action potentials not carried by calcium. These drugs may also affect other parts of the action potential, such as later occurring outward currents, and thus the drugs influence "ion gates" of membranes, not just the influx of calcium.

Specific clinical indications for each drug have evolved. For example, since verapamil has a more profound influence on the calcium current of the sinoatrial (SA) and AV nodes, this drug has been most useful in treat-

ment of supraventricular tachyarrhythmias, which are often caused by reentry through the AV node. In contrast, nifedipine in an intact cardiovascular system has less influence on the SA node and no effect on AV conduction time. Therefore, nifedipine might be used when a calcium channel blocker is desirable in a situation where depression of AV conduction is undesirable.

Clinical pharmacology
In-depth discussions of the clinical pharmacology of verapamil, nifedipine, and diltiazem have been published.[5-8] Information is more complete for verapamil and nifedipine.

Verapamil is 90% absorbed from the gastrointestinal tract.[9,10] However, its bioavailability after oral administration is 10% to 22%, indicating extensive first-pass metabolism in the liver. The oral dose must be at least eight to ten times the intravenous dose to cause comparable plasma levels and similar physiologic effects.

After oral or intravenous administration of verapamil, plasma levels decline biexponentially, with an initial rapid or distribution phase (alpha phase) of 18 to 35 minutes followed by a slower elimination phase (beta phase) with a half-life of 170 to 440 minutes.[9] Of

The dose of calcium channel blocker used for each individual patient must be titrated according to clinical circumstances.

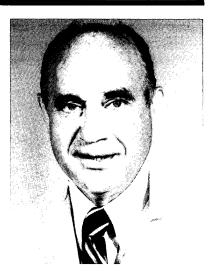an intravenous or oral dose, 70% is excreted in the urine and 16% in the feces. Intact verapamil is 90% protein bound.[9]

Electrophysiologic effects appear within two hours and peak at five hours after a single oral dose of verapamil.[11] After an intravenous dose, the negative dromotropic effect appears in one to two minutes, the peak effect occurs at 10 to 15 minutes, and an effect is still detectable at six hours. Preferential uptake and binding of verapamil by AV nodal tissues may occur, because the depressant effect on the AV node persists longer than the hemodynamic effects.[12,13]

The percentage of verapamil excreted in the urine as unchanged drug is 3% to 4%.[14] The major metabolic reaction of verapamil is cleavage of the C-N-C bond by N-dealkylation, preferentially at the carbon atom belonging to the shorter side chain. Verapamil and its N-dealkylated metabolites are further metabolized by O-demethylation. Twelve metabolites have been identified, norverapamil being the major one. The plasma levels of verapamil's metabolites exceed the plasma level of intact verapamil during long-term treatment.[9,14] These metabolites should be further investigated to assess their contribution to the actions of vera-

pamil.

Nifedipine is 90% absorbed from the gastrointestinal tract and from sublingual administration and has higher bioavailability than verapamil or diltiazem.[15] Buccal administration is a more rapid method of achieving peak blood concentrations (three minutes) than oral administration (one to two hours). The plasma half-life of nifedipine is four hours. Intact nifedipine is 90% protein bound.

Nifedipine has rapid distribution, with increased concentrations in liver, kidney, and muscle. Concentrations are higher in heart muscle than in skeletal muscle. Nifedipine is extensively metabolized to inert products (a hydroxycarboxylic acid and a lactone).[16] Of metabolized nifedipine, 80% is eliminated via the kidney. The other 20% is presumed to be excreted through the gastrointestinal tract.

Pharmacokinetics have been described in less detail for diltiazem than for verapamil and nifedipine.[17,18] Controversy exists as to the extent of protein binding, with some investigators reporting that intact diltiazem is 80% protein bound. The plasma half-life is four hours. Diltiazem may be extensively deacetylated. Some reports indicate 80% excretion of diltiazem and its metabolites in the urine. However, there are also reports that 60%

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is metabolized by the liver and 40% is excreted by the kidneys.

Dosage and drug interactions
Reported doses of calcium channel blockers vary considerably, with a tendency in recent years toward use of higher doses. It should be emphasized that the dose of drug used for each individual patient must be titrated according to clinical circumstances. Oral doses of verapamil vary from 80 to 320 mg every six to eight hours. Oral, buccal, and sublingual doses of nifedipine range from 10 to 60 mg every four to eight hours.

Most of the adverse effects of calcium channel blockers reported in the literature are cardiovascular.

Oral doses of diltiazem vary from 60 to 120 mg every six to eight hours. The initial intravenous dose of verapamil used for treating supraventricular tachyarrhythmia is 0.15 mg/kg (maximum dose 10 mg) injected over a one-minute period under ECG and blood pressure monitoring. The intravenous dose ranges from 0.005 to 0.015 mg/kg for nifedipine and from 0.075 to 0.15 mg/kg for diltiazem. Table 1 summarizes the dosage and indications for use of these agents.

Details of many drug interactions with the calcium channel blockers are incomplete. Nifedipine has been reported to be compatible with nitrates, beta-adrenergic blocking drugs, digoxin, diuretics, antihypertensives, anticoagulants, and hypoglycemics.

Because of verapamil's preferential action on the SA and AV nodes, concomitant therapy with drugs that also depress nodal conduction, such as digitalis or beta-adrenergic blockers, must be undertaken with caution. Complete AV block, sinus standstill, ventricular asystole, and even death may result from simultaneous use of these drugs in patients with underlying disease of the SA or AV node.

Adverse effects may result if verapamil is used with reserpine[19] or disopyramide (Norpace).[20] Verapamil also produces a significant increase in serum digoxin concentration.[21] Therefore, it should be used cautiously in patients receiving digitalis. Verapamil and nifedipine may interfere with platelet function. Additional investigations of potential drug interactions with the calcium channel blockers are needed.

Adverse effects
The majority of adverse effects of calcium channel blockers reported in the literature are cardiovascular. Verapamil may cause hypotension, shock, development or worsening of congestive heart failure, pulmonary edema, sinus bradycardia, various degrees of AV block including complete block, ventricular arrhythmias, sinus standstill, ventricular asystole, and even death.[19,22-36] Verapamil should not be used in treating patients with supraventricular tachyarrhythmias who have SA disease or preexisting disease of the AV node,[22,37-45] nor should it be used to treat patients with atrial fibrillation or atrial flutter associated with the Wolff-Parkinson-White syndrome.[46-48]

Gastrointestinal side effects of verapamil are constipation, nausea, and vomiting. CNS effects are light-headedness, headache, vertigo, weakness,

All calcium channel blockers are contra-indicated in hypotension, with the possible exception of verapamil used in treating a patient with hypotension due to a supraventricular tachyarrhythmia.

Table 1. Calcium channel blockers: dosage and indications

Drug	Route of administration	Dosage	Approved indications
Verapamil (Calan, Isoptin)	Oral	80-320 mg every 6-8 hr	Angina at rest (vasospastic), unstable angina, chronic stable angina
	Intravenous	Initial dose 0.075-0.15 mg/kg; repeat dose 0.15 mg/kg	Supraventricular tachyarrhythmias
Nifedipine (Procardia)	Oral	10-60 mg every 4-8 hr	Angina at rest (vasospastic), unstable angina, chronic stable angina
	Intravenous	0.005-0.015 mg/kg	
Diltiazem (Anginyl)	Oral	60-120 mg every 6-8 hr	Approval pending
	Intravenous	0.075-0.15 mg/kg	

anxiety or nervousness, and mental confusion. Other adverse effects include dyspnea, ankle edema not associated with congestive heart failure, pruritus, flushing, and burning in the limbs.

Oral administration of verapamil, 180 to 480 mg daily (mean 330), to 21 patients with supraventricular tachyarrhythmias resulted in four patients (19%) stopping the drug within 30 days because of adverse effects and six patients (29%) discontinuing it within the same period because of ineffectiveness.[47] Seven patients received verapamil for 14 to 23 months. Early side effects included nausea, vomiting, and light-headedness (four patients). Later adverse effects included ankle edema not associated with congestive heart failure (five patients), constipation (three patients), and postural hypotension (one patient). Other side effects reported from verapamil include hepatotoxicity[49] and hyperprolactinemia and galactorrhea.[50]

Oral administration of nifedipine, 40 to 160 mg daily (mean 64), for a mean duration of nine months to 127 patients with angina pectoris attributed to coronary artery spasm resulted in side effects in 39% of patients.[51] Five percent discontinued the drug because of adverse effects, most commonly dizziness, flushing, and headache. Pedal edema, hypotension, paresthesias, weakness, muscle cramps, nausea, palpitations, rash, and other side effects also occurred.

AV nodal conduction disturbances may accompany intravenous administration of diltiazem. Rash, dizziness, headache, flushing, and gastrointestinal discomfort have also been reported. Some reports suggest that side effects are lower with diltiazem than with other calci-
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Intravenous verapamil is the drug of choice in treating paroxysmal supraventricular tachycardia unresponsive to vagal maneuvers.

um blockers, since the agent may more selectively affect the coronary vasculature rather than the peripheral arterial tree, which results in activated reflexes.

All of the calcium channel blockers are contraindicated in hypotension, with the possible exception of verapamil used in treating a patient with hypotension resulting from a supraventricular tachyarrhythmia. Caution should be used in treating patients with a combination of a calcium channel blocker and other drugs with a high extent of protein binding, such as phenytoin (Dilantin) or warfarin, until appropriate data are available. Caution should also be used in treating patients with a combination of a calcium channel blocker (especially verapamil) and antiarrhythmic drugs of other classes until drug interaction studies have been reported.

Treatment of toxicity

Hypotension should be treated with 10 to 20 ml of a 10% calcium gluconate solution administered intravenously and, if necessary, with infusion of a catecholamine vasopressor agent. Marked sinus bradycardia, sinus standstill, advanced AV block, and ventricular asystole should be treated with intravenous infusion of isoproterenol

(Isuprel), cardiopulmonary resuscitation (if necessary), and temporary ventricular pacing (if necessary). Congestive heart failure should be treated with diuretics, intravenous administration of 10 to 20 ml of a 10% calcium gluconate solution, and intravenous infusion of dopamine or isoproterenol (if needed). Catecholamines such as isoproterenol and epinephrine counteract verapamil's depressant effects on the SA and AV nodes better than atropine.[22,23,38,44,52] Beta-adrenergic agonists reverse verapamil's depressant effects by increasing cyclic adenosine monophosphate, increasing the magnitude of the slow inward current.[53]

Use as antiarrhythmic agents

Nifedipine has no intrinsic antiarrhythmic properties. Few data are available on the role of diltiazem in treatment of arrhythmias. However, verapamil is useful in treatment of supraventricular tachyarrhythmias.

SITES OF ACTION—Verapamil acts on the following sites in the heart.

SA NODE—Verapamil depresses the discharge rate of the SA node because normal impulse formation in the SA node is slow channel dependent.[37-39] This depressant effect is not mediated via the autonomic

nervous system, since it occurs in the presence of autonomic blockade with propranolol (Inderal) and atropine.[37] The reduction in SA node automaticity by verapamil can be reversed by epinephrine and may result from a decrease in the rate of spontaneous diastolic depolarization or from a shift in threshold potential to less negative values.[38] In the absence of a diseased SA node, this decrease in SA node frequency is nullified by the reflex tachycardia caused by hypotension due to peripheral vasodilatation.[54,55] With an intact cardiovascular system, the sinus rate after verapamil, nifedipine, or diltiazem administration may be variable, depending on the degree of reflex increase in sympathetic tone. Diltiazem may be less likely to cause reflex heart rate changes. Verapamil prolongs SA node recovery time in patients with the sick sinus syndrome.[22,40,41]

ATRIA—Verapamil does not affect the rate of the depolarization or repolarization phase of the action potential in atrial fibers,[38,42,43] nor does it change intraatrial conduction time.[39,41,43,44] This drug may suppress slow-channel-dependent action potentials from diseased atrial muscle fibers.[56]

AV NODE—Verapamil reduces the amplitude of action potentials in the upper and mid por-

Intravenous verapamil effectively reduces the rapid ventricular rate in patients with atrial fibrillation.

tions of the AV node without significantly decreasing the maximal diastolic potential.[38] This drug prolongs AV node conduction time (because the PR interval is lengthened due to a prolonged AH interval) without affecting the PA, HV, QRS, or QTc interval and lengthens the functional and effective refractory periods of the AV node.[22,23,37-39,41,43,44,57-59]

Verapamil has minimal effect on anterograde and retrograde conduction through an anomalous pathway in the Wolff-Parkinson-White syndrome but may enhance anterograde conduction over the accessory pathway in patients with atrial fibrillation or atrial flutter associated with this syndrome.[46-48] Verapamil increases AV node refractoriness by direct action on slow-channel fibers in the AV node.[37] The prolongation of AV nodal conduction time by this drug is largely independent of the autonomic nervous system.[37,60] The AV node is more susceptible to depression by verapamil when beta receptors are blocked or local catecholamine stores are depleted.[19]

HIS-PURKINJE SYSTEM—Verapamil does not significantly affect the rate of the depolarization or repolarization phase of the action potential in His-Purkinje fibers[39,61] and does not change the HV or QRS inter-

val.[39,41,43,44,58]

VENTRICLES—Verapamil does not significantly affect the rate of the depolarization or repolarization phase of the action potential in ventricular muscle fibers,[42] nor does it affect intraventricular conduction time.[39,41,43,44] This drug may suppress slow-channel-dependent action potentials from diseased ventricular muscle fibers.[62]

EFFECTS ON ARRHYTHMIAS— Verapamil has been used in treating the following types of arrhythmias.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA—Intravenous verapamil is the drug of choice in treating paroxysmal supraventricular tachycardia unresponsive to vagal maneuvers. Within minutes, it converts paroxysmal supraventricular tachycardia with or without an associated extranodal pathway to sinus rhythm (about 80% of cases) or decreases a rapid ventricular rate (about another 10% of cases).[13,23,24,26-28,46-48,58,59,63-69]

Verapamil is effective in treatment of paroxysmal supraventricular tachycardia because it prolongs AV nodal conduction and increases the AV nodal refractory period. Paroxysmal supraventricular tachycardia-due to AV nodal reentry responds better to intravenous verapamil than does paroxysmal supraventricular tachycardia due to

an ectopic atrial focus. Verapamil also terminates AV nodal reentry more successfully than SA nodal reentry.[47]

The mode of conversion of paroxysmal supraventricular tachycardia to sinus rhythm by verapamil varies. The following may occur: (1) abrupt termination of the supraventricular tachycardia, (2) slight reduction in the ventricular rate followed by a short pause before conversion to sinus rhythm, (3) AV dissociation with an AV junctional escape rhythm followed by sinus rhythm, (4) transient atrial fibrillation before sinus rhythm, (5) ventricular premature depolarizations before conversion to sinus rhythm, and (6) alternation of cycle length before conversion to sinus rhythm.[13,28,58,63,68]

Intravenous verapamil has been beneficial in treatment of supraventricular tachyarrhythmias after recent myocardial infarction.[70] However, verapamil's intrinsic negative inotropic effect on the myocardium is dose related,[10,45] and if ventricular function is impaired, high doses may precipitate congestive heart failure.[25]

The incidence of placebo effect in the therapy of paroxysmal atrial tachycardia is very high.[64] Therefore, a placebo control must be used in studies evaluating the efficacy of drug

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By treating coronary vasospasm, the calcium channel blockers may improve ventricular arrhythmias associated with myocardial ischemia.

treatment of this arrhythmia.

Use of oral verapamil as a single drug or in combination with other drugs to prevent recurrences of paroxysmal supraventricular tachycardia appears promising.

PAROXYSMAL ATRIAL TACHYCARDIA WITH AV BLOCK—In one study,[71] paroxysmal atrial tachycardia with AV block initially converted to sinus rhythm in 10 of 14 patients (71%) after oral administration of verapamil, 40 to 80 mg every three hours. Six patients were maintained in sinus rhythm. Double-blind, randomized studies comparing oral verapamil with placebo for efficacy in treatment of paroxysmal atrial tachycardia with AV block need to be performed before use of verapamil is considered in this setting.

ATRIAL FIBRILLATION—Intravenous verapamil rarely converts atrial fibrillation to sinus rhythm but is effective in decreasing a rapid ventricular rate in patients with this arrhythmia.[12,13,23,47,58,63-66,72] Verapamil lengthens AV nodal conduction time and also prolongs the functional and effective refractory periods of the AV node.[22,23,37-39,41,43,44,57-59] These electrophysiologic effects explain the efficacy of verapamil in reducing the ventricular rate in patients with atrial fibrillation. In patients with congestive

heart failure and atrial fibrillation or atrial flutter, higher doses of verapamil cause higher plasma levels of drug but less decrease of the ventricular rate than smaller doses in patients without congestive heart failure.[72]

Oral verapamil is not effective in preventing recurrent episodes of atrial fibrillation.[47] However, oral verapamil may be useful as an adjunct to digitalis in controlling a rapid ventricular rate at rest and during exercise in patients with chronic atrial fibrillation.[73,74]

ATRIAL FLUTTER—Intravenous verapamil is effective in slowing a rapid ventricular rate in patients with atrial flutter and occasionally converts atrial flutter to atrial fibrillation or to sinus rhythm.[12,13,23,47,58,63-66,70,72] Verapamil does not change the rate of atrial flutter. By increasing AV nodal conduction time and the functional and effective refractory periods of the AV node,[22,23,37-39,41,43,44,57-59] this drug decreases the ventricular rate in patients with atrial flutter.

Oral verapamil is not effective in preventing recurrent episodes of atrial flutter.[47] However, it may be useful as an adjunct to digitalis in controlling a fast ventricular rate in patients with this arrhythmia.

WOLFF-PARKINSON-WHITE SYNDROME—Intravenous verapamil

is effective in converting paroxysmal reciprocating supraventricular tachycardia with or without an associated extranodal pathway to sinus rhythm.[13,23,24,26,28,46-48,59,63,64] Verapamil does not affect anterograde or retrograde conduction through the accessory pathway or refractoriness of the accessory pathway.[46-48] By prolonging AV nodal conduction and AV nodal refractoriness, this drug converts paroxysmal reciprocating supraventricular tachycardia with an associated extranodal pathway to sinus rhythm.

Verapamil should not be used in treating patients with atrial flutter or atrial fibrillation associated with the Wolff-Parkinson-White syndrome.[46-48] By prolonging AV nodal conduction, verapamil reduces retrograde concealed penetration of the accessory bypass tract during atrial flutter or atrial fibrillation, which may enhance anterograde conduction over the accessory pathway, increasing the ventricular rate.

The efficacy of oral verapamil when used as a single drug or in combination with other drugs in preventing or decreasing recurrences of paroxysmal reciprocating supraventricular tachycardia associated with manifest or concealed Wolff-Parkinson-White syndrome needs to be investigated by

double-blind, randomized studies using placebo. Results cannot be predicted from the response to the intravenous form.[47]

MULTIFOCAL ATRIAL TACHYCARDIA—Intravenous verapamil is not very effective in treatment of multifocal atrial tachycardia.[64] At the present time, there is no effective drug for this arrhythmia.

VENTRICULAR ARRHYTHMIAS—Intravenous verapamil is not very effective in treatment of premature ventricular depolarizations or ventricular tachycardia.[13,23,58,63-65,75] This drug infused five hours after initial plasma creatine kinase elevation following coronary occlusion in dogs did not augment flow in ischemic tissue, limit the extent of myocardial infarction, or decrease the incidence or severity of premature ventricular depolarizations.[76] However, by treating coronary vasospasm, the calcium channel blockers can improve ventricular arrhythmias associated with myocardial ischemia.

Conclusions

Intravenous verapamil (Calan, Isoptin) has therapeutic advantages over beta-adrenergic blockers in treatment of paroxysmal supraventricular tachycardia, atrial flutter with a fast ventricular rate, or atrial fibrillation with a fast ventricular rate in patients with chronic obstructive pulmonary disease[77,78] or decreased myocardial reserve.[55] This drug should not be used in treating patients with supraventricular tachyarrhythmias who have sinoatrial disease or preexisting disease of the atrioventricular node.[22,37,39,40-45] Other contraindications to intravenous verapamil are cardiogenic shock, hypotension (except when resulting from the tachyarrhythmia), very severe left ventricular dysfunction, suspected digitalis toxicity, and atrial flutter or atrial fibrillation associated with the Wolff-Parkinson-White syndrome.

Intravenous verapamil is the drug of choice in treating paroxysmal supraventricular tachycardia with or without an associated extranodal pathway. This agent is also effective in slowing a rapid ventricular rate in atrial fibrillation or atrial flutter. Oral verapamil may be useful as an adjunct to digitalis in controlling a rapid ventricular rate at rest and during exercise in patients with atrial flutter. **PGM**