EDITORIALS

Welcome—The Calcium Channel Blockers

The calcium channel blocking agents which have now become available in this country have great potential use in patients with combined cardiac and pulmonary disorders. Thus, it is especially appropriate for readers of this journal, which deals with both cardiac and pulmonary disorders, to be aware of the therapeutic potential of these drugs.

Clinical experience with the calcium channel blockers around the globe has already been extensive. However, use of the drugs in the United States will officially be limited to specific utilization based upon trials with clear results which are appropriately controlled and executed. However, just as when propranolol was released for treatment of hypertension and cimetidine for peptic ulcer, we can expect many practitioners to use these drugs to their full theorized advantage. Therefore, we may expect the drugs might be used in situations beyond their objectively proven and officially approved use as soon as they become widely available.

We can expect these drugs to be especially appropriate for certain cardiovascular disorders in patients with pulmonary disease, since the calcium channel blockers do not have beta-adrenergic blocking activity. The predominant action of the calcium channel blockers is to oppose the calcium fluxes at specific cellular sites such as membranes. Since calcium is the critically important ion in cardiovascular function, the impact of impeding calcium fluxes results in numerous effects. The calcium channel blockers can be expected to interfere with electrical depolarization of the cells, the contractile process, coronary tone, peripheral vascular tone, intracellular metabolic processes and possibly even the process of cellular death which is dependent upon calcium influx. The drugs which are likely to receive earliest widespread clinical utilization in the United States are verapamil, (Isoptin—Knoll Pharmaceutical Company, Calan—G. D. Searle & Company); nifedipine (Procardia—Pfizer, Inc.); diltiazem (Cardiem—Marion Laboratories).

Specific clinical indications for each drug are rapidly evolving. For example, since verapamil has a more profound influence on the calcium current of the sinoatrial (SA) and atrioventricular (AV) node, this drug has been most useful in the treatment of supraventricular tachyarrhythmias which are often caused by re-entry through the AV node. Verapamil is clearly advantageous compared to current therapies for paroxysmal atrial tachycardia in patients with respiratory failure. Unfortunately, the drug is not effective against multifocal atrial tachycardia. In contrast, nifedipine in an intact cardiovascular system has less of an influence on the SV and AV node. This drug may be advantageous for treatment of patients with angina and obstructive lung disease who cannot tolerate beta-adrenergic drugs or who have AV conduction disease and cannot tolerate verapamil.

The calcium channel blockers will have widespread use in the treatment of supraventricular arrhythmias, variant angina, and chronic angina pectoris. Additional potential uses may be for the treatment of hypertrophic cardiomyopathy, systolic and pulmonary hypertension, and for the prevention of ischemic myocardium during evolving infarction or cardiopulmonary bypass.

ARRHYTHMIAS

Verapamil is the most effective of the drugs for supraventricular tachyarrhythmias, and intravenous verapamil for paroxysmal atrial tachycardia is the first approved use of the calcium channel blockers in the United States. This form of treatment for re-entry paroxysmal atrial tachycardia will supersede all previous pharmacologic treatments, as well as cardioversion. Several words of caution are in order. Verapamil may be deleterious in patients with pre-excitation syndromes with atrial flutter or fibrillation, causing enhanced anomalous tract conduction. The potential of verapamil to cause AV block may be exaggerated in the presence of underlying conduction disease such as in patients with sick sinus syndrome or when used concurrently with other drugs that depress AV function (eg,
digitalis or beta-adrenergic blocking drugs). Oral verapamil therapy has been successful in some preliminary studies for prevention of paroxysmal supraventricular tachycardia, but its superiority over other agents should be confirmed in double-blind controlled studies. Verapamil may be useful in slowing atrial fibrillation. In atrial flutter, enhanced AV block may be achieved, but conversion occurs only infrequently. Nifedipine and diltiazem are not specifically efficacious for treatment of supraventricular tachyarrhythmias.

The calcium channel blockers are not specifically effective as sole therapy of ventricular dysrhythmias. Nevertheless, the drugs may have an ameliorating influence on ischemic myocardium and coronary spasm which could result in an indirect salutary influence on ischemic ventricular dysrhythmias.

**Variant Angina—Prinzmetal's Angina**

In numerous studies, the calcium channel blockers have been found to be effective for the treatment of variant angina caused by coronary vaso-spasm. This has been proved in double-blind randomized studies with comparison to nitroglycerine. Although nitrates are often effective for variant angina, the calcium channel blockers offer advantages for difficult cases, are longer acting, and are effective when nitrates are not. Nifedipine, diltiazem and verapamil are all effective for treatment of variant angina, and the advantages of one of these agents over the other has not yet been satisfactorily displayed.

**Angina Pectoris**

Current medical therapies for angina pectoris frequently meet with failure. There are numerous situations in which patients cannot tolerate conventional therapy with beta-adrenergic blocking drugs and nitrates, or when surgery may not be advisable. Nifedipine, verapamil and diltiazem have been shown to be effective in treatment of chronic ischemic syndromes even when evidence for coronary spasm is not present. With mild or moderate left ventricular dysfunction, the vasodilating afterload-reducing influences of the drug compensate for any negative inotropic effects which may be obvious in the laboratory setting in isolated preparations. With very high filling pressures, the drugs have been reported on occasion to further reduce mechanical performance. It has been suggested that nifedipine in clinical doses has less potential to cause negative inotropic effects than the other calcium channel blockers. Nifedipine may be better suited for combined therapy with beta-adrenergic blocking drugs or digitalis since, in usual doses, it does not effect AV conduction. It has not been established whether these agents are more effective than currently available treatments for patients with coronary artery disease or unstable angina.

**Preservation of Ischemic Myocardium**

The theory of using these agents during evolving myocardial infarction or for preservation of ischemic myocardium during cardiopulmonary bypass is attractive. Transmembrane calcium influx is associated with early structural damage and transmembrane calcium influx is also important to the pathophysiology of coronary perfusion and also reperfusion. These phenomena may be present during evolving infarction and also during cardiopulmonary bypass. These agents may allow ischemic tissue to sustain metabolic health longer during hypoxia, reduce myocardial oxygen requirements, cause coronary vasodilatation, and enhance collateral flow. On the other hand, the potential to impair AV conduction, reduce blood pressure and therefore coronary perfusion pressure, and the potential negative inotropic effects in patients with severe contractile abnormalities, suggest caution when using these drugs during evolving infarction or as a cardioplegic agent. Proving salutary effects in the clinical setting has been difficult in part related to obtaining objective measures of infarct size in patients, determining the metabolic health of tissues undergoing cardioplegia, finding the proper dose, and initiating therapy early in the case of acute myocardial infarction. Experimental studies using nifedipine as an adjunctive cardioplegic agent during cardiopulmonary bypass surgery have been promising. Nevertheless, no properly controlled clinical studies are available which warrant the use of these agents solely for preservation of ischemic myocardium.

**Hypertrophic Cardiomyopathy**

Verapamil, in preliminary clinical studies, has reduced the basal left ventricular pressure gradient present in these patients, improved exercise capacity, and has caused subjective improvement with fewer side effects than beta-adrenergic blocking drugs. However, adverse effects resulting in serious complications have occurred in patients with hypertrophic cardiomyopathy and the following: 1) high pulmonary capillary wedge pressures in the presence of left ventricular outflow obstruction; 2) a history of orthopnea or paroxysmal nocturnal dyspnea in the presence of left ventricular outflow obstruction; 3) sick sinus syndrome or AV junctional
disease unless pacemakers are implanted; 4) low systolic blood pressure. Some animal studies even suggest that these drugs may be useful in retarding other cardiomyopathic conditions and this is an exciting possibility. Further studies using these drugs for treatment of hypertrophic and other cardiomyopathies are underway.

**OTHER POTENTIAL USES**

Nifedipine may be useful in treatment of systemic hypertension and also in hypertensive emergencies. These agents may be the most efficacious and logical choices as adjunctive drugs for systemic hypertension, especially when patients are being treated with the medications for other indications. Further comparative studies using calcium antagonists for treatment of systemic hypertension are needed. Verapamil and nifedipine have been shown to reduce pulmonary pressure in patients with pulmonary hypertension. In patients with chronic air flow obstruction and acute respiratory failure, nifedipine vasodilates pulmonary vessels constricted by hypoxia without causing a reduction in arterial oxygenation. Although nifedipine and verapamil do not have intrinsic bronchodilator properties in unstimulated airways, they may blunt the development of airway obstruction following exercise in asthmatic patients. We hope the role of these drugs in asthma and acute and chronic pulmonary hypertension will be better defined in the near future.

The vasodilating properties of the drug may be useful in treatment of congestive heart failure, aortic and mitral insufficiency, although careful monitoring of ventricular performance is required, in view of the potentially negative inotropic effect. Verapamil and nifedipine may interfere with platelet function. The role of these drugs in sudden cardiac death is not yet defined. Non-cardiopulmonary uses such as for treatment of cerebral vasospasm, gastrointestinal, obstetric and gynecologic disorders requires further investigation.

**CONCLUSIONS**

This new class of drug has some clear advantages over currently used medications for treatment of specific cardiovascular disorders. One of the major advantages may be that these drugs are useful in the presence of chronic obstructive lung disease or in situations where beta-adrenergic blocking agents cannot be used. Calcium channel blockers may allow more effective treatment of paroxysmal atrial tachycardia and angina pectoris in patients with chronic obstructive lung disease. The agents may produce fewer unpleasant side effects than beta-adrenergic blocking drugs or nitrates, although this needs further confirmation. Initial euphoria must be tempered by the proof of substantial improvement in morbidity and mortality. Nevertheless, the use of this new class of drugs is a welcome addition to our armamentarium.

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**High Frequency Ventilation**

A Passing Fancy?

Over the last two years, interest in high frequency ventilation (HFV) has increased considerably. The technique is not really new, having been described in Sweden some 15 years ago. Originally developed to aid ventilation during bronchoscopy and laryngeal procedures, HFV now has much broader implications.

All modes of HFV are not the same. The different systems of delivery have distinct characteristics. High frequency jet ventilation, described in this issue by Schuster and colleagues (see page 682), delivers each breath through a narrow orifice such as a 14- or 16-gauge intracath. The accelerated flow, operating on the Bernoulli principle, entrains humidified gas, which also enhances tidal volume. The usual frequency is 100-900/min. High frequency positive pressure ventilation is similar, but operates without entrainment. Both methods require a circuit with minimal compressible volume to minimize the loss of gas in the circuit.

High frequency oscillation differs greatly from those two methods. Usually, a piston pumps a set volume of gas into the airway, first in one direction, then in the other. There is no bulk flow. Oxygen is added at a rate consistent with metabolic demands; an absorber or a bypass circuit removes carbon dioxide. This system has so far performed best at rates between 900 and 2,000/min.

The principle effects of HFV compared to the conventional ventilation are reductions of peak inflation and mean airway pressure. Possible benefits include minimal pulmonary barotrauma and less interference with cardiac output.

Several theories attempting to explain the mechanism of HFV have been advanced. However, precise information is still scarce. The rapid rate, small volume, and high flow make difficult the tracing of gas distribution.

Although heralded as a major technologic break-