INTRODUCTION

Whereas the beta blocking drugs were the "drugs of the 70's", it may be fairly said that the calcium blocking drugs are the "drugs of the 80's" (1). In view of the ubiquitous nature of the calcium ion as a second or third messenger in mediating cell activity, it is not surprising that drugs which interfere in calcium homeostasis may be useful in a variety of disease states, particularly those involving excess cardiovascular activity.

Pharmacology

Although these drugs have been referred to as "calcium antagonists", in fact, they really are not pharmacologic antagonists of the calcium ion. Rather, they interfere with the passage of calcium ions through the cell membrane as the primary mode of action (there may also be some effect on calcium channels on interior cellular membranes as well, but this is still controversial). Since the influx of calcium ion from the high concentration in the extracellular fluid through the cell membrane to raise the normally low concentration intracellularly (less than 10^-6 M) is the major event initiating contraction of all muscle, it is logical that the major use of calcium channel blocking (CCB) drugs involves interference with the contraction of various types of muscle. It is also in keeping with the physiology that effects of channel blockers on skeletal muscle are minimal since skeletal muscle does not depend to nearly as great an extent on calcium ion influx through the cell membrane for initiation of its effect.
Consequently, CCB's primarily affect cardiac and smooth muscle contraction as the mechanism of their pharmacologic action. In addition, the calcium ion provides the major current for the automatic and conducting tissues of the heart (S-A and A-V nodes) so that these drugs also have an effective antiarrhythmic action. Inasmuch as the primary effect is not on the electrical activity of actual heart muscle, or the Purkinje fibers, the major antiarrhythmic efficacy of these drugs is in supraventricular arrhythmias, particularly paroxysmal supraventricular arrhythmias.

Unlike the beta adrenergic blocking drugs where there is practically a rigid structure activity relationship, several different chemical formations have potent calcium channel blocking activities. The original papaverine derivatives, verapamil and D-600, were the prototype CBB drugs. However, most of the recent newer drugs are dihydroperidines of the nifedipine type. The diphenyl alkylamines such as diltiazem also belong to this class of drugs. Verapamil and nifedipine are the opposite ends of the spectrum (Table 1). Nifedipine is primarily a vasodilator drug with minimal effects in intact animals and humans on cardiac muscle and electrophysiology. Verapamil, on the other hand, although possessing vasodilator properties, also is a potent antiarrhythmic and depresses cardiac muscle directly as well. Diltiazem appears to be intermediate between the two, possessing all the CCB properties but producing more prominent vasodilation than nifedipine.

Uses

The clinical uses for these drugs are remarkably similar to those of the beta blockers. As with the beta blockers, the first FDA approved indication was for the treatment of arrhythmias, in this case supraventricular arrhythmias. In particular, verapamil, and to a lesser extent diltiazem, is currently the drug of choice for conversion of paroxysmal supraventricular arrhythmias. As with the beta blockers, the second approved indication was for the treatment of ischemic heart disease. The major advantage of these drugs over the beta blockers for the treatment of IHD is that they are coronary vasodilators and hence, in addition to decreasing