Calcium Antagonist Drugs

Calcium antagonist drugs are relatively new to the clinical pharmacologic arena. They are timely additions, not only because of their potential beneficial effects, but also because they facilitate research into a better understanding of excitation-contraction-coupling, in particular into details of the initiation and maintenance of contraction of vascular smooth muscle. It is in this latter process that the role of the movement of calcium ion across cell membranes is crucial.

It is curious how medical interest in coronary spasm has waxed and waned over the centuries. The differentiation between classical angina pectoris—ischemia being caused by an inability to satisfy an increased demand for myocardial oxygen—and unstable angina pectoris, in which ischemia results from a reduction in coronary flow because of spasm in the absence of any increased demand, is crucial to understanding the mechanism and management of cardiac pain. Perhaps one of the earliest convincing descriptions of unstable angina pectoris, written in the early part of the 17th century, was not recorded by a physician at all, but by the Earl of Clarendon, Lord High Chancellor of England, and pre-dated Heberden and Parry by many years. More recently and largely a result of the studies of Masani and his colleagues in Pisa, the importance of coronary spasm as the cause of unstable angina pectoris has been confirmed; the trigger mechanism for the onset of such spasm, however, remains unclear, but a good deal of effort is now being devoted to unraveling this mystery.

Calcium flux has an important role in vasoactive change. The ability to block such shifts, fundamental to the effects of drugs such as diltiazem, is crucial to a better understanding not only of the cause of inappropriate coronary arterial spasm, but also its clinical management.

The conference recently held in Mexico on calcium antagonist drugs, particularly diltiazem, with generous support from Marion Laboratories, was not only timely but also a unique opportunity for discussing both the basic and clinical aspects of these drugs. As is apparent from the proceedings of the symposium which follows, the conference was an outstanding success. Investigators from many diverse fields and disciplines were able to exchange ideas and to provide new information. Perhaps the true success of the symposium, as with other such multidisciplinary conferences, will ultimately be gauged by newer investigational paths suggested by the lively discussions that followed the formal presentations of scientific data.

Although we now have a better understanding of the various effects of the calcium ion and its role in the initiation and contraction of smooth muscle, much detail yet remains to be discovered at the cellular level.

Equally uncertain is the clinical role of diltiazem and other calcium antagonist drugs. Up to the present they have been used largely for managing coronary arterial spasm, stable angina pectoris and certain forms of cardiac dysrhythmias, particularly reentrant supraventricular tachycardias. Since they also exert a powerful effect on tone of the peripheral vasculature they may have an additional important therapeutic role in refractory cardiac failure, in enhancing cerebral flow and even in the management of hypertrophic cardiomyopathy with obstruction.

Before we abandon more traditional therapy for angina pectoris, both stable and unstable, the clinical role of the newer agents will have to be more precisely defined. The inter-relationship between peripheral and central hemodynamic effects has not yet been clearly separated and certain of the calcium antagonist drugs are known to be negatively inotropic. Fortunately, it seems that the effect on calcium flux is greater in vascular smooth muscle than in the myocardium; thus, important cardiac depression may be more theoretical than real. This has yet to be determined, however, as has the true nature of drug interactions when calcium antagonists are used together with other medications. Thus, not only the basic researcher, but also the clinician will have an important role in the better understanding of the action and uses of diltiazem and other calcium antagonist drugs.

It can be predicted with confidence that only such combined approaches at the basic and clinical levels will provide the intellectual and investigational milieu for a better understanding of the effects of calcium antagonist drugs leading to additional therapeutic modalities that are so badly needed. Marion Laboratories and the organizers of the symposium are to be congratulated for providing the opportunity for the dissemination of new knowledge important both to clinicians and basic scientists and leading to newer investigational and therapeutic approaches.

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