EDITORIAL COMMENT

CALCIUM ANTAGONISTS—FUTURE USES

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KEY WORDS. Calcium antagonists, ischemic heart disease, central nervous effects, calcium

There are a considerable number of publications every month on new results with calcium antagonists. Part of the literature deals with new drugs to confirm their efficacy and safety within the already established indications for calcium antagonists. However, growing attention now is dedicated toward the exploration of new indications both for the existing as well as the more recently developed compounds.

The newer calcium antagonist drugs pharmacologically resemble closely the already well-known compounds but differ concerning strength of receptor binding as well as in their pharmacokinetic profile.

New Pharmacologic Properties

In particular, the higher lipophilicity of some of the newer compounds makes it possible to reach concentrations required to also affect receptors that are outside the water distribution space (like receptors at neuronal tissue structures). The latter is important in so far as the search for new applications is based on recent experimental findings differentiating among at least three distinct types of receptors: a slowly opening (l-type), a fast opening (t-type), and the receptor regulating calcium entry at neuronal structures (n-type) [1].

Calcium antagonists affect only the l-type receptors. On the one hand this could offer an explanation for the observation that blood pressure is not reduced below a physiologic level (if heart rate is not intrinsically suppressed), e.g., even with high doses of the dihydropyridine-type drugs. A compensation of l-receptor suppression by the t-receptor-mediated Ca movement could be responsible for this. The selectivity of channel blocking by calcium antagonists result in an inhibition of only a certain part of the calcium currents, which may also be responsible for the slow achievement of the full therapeutic effect. In contrast to true vasodilators, the pharmacologic effectiveness increases with continuous dosage of calcium antagonists.

Even more important for a possible expansion of the range of indications was the recent discovery of an interference by Ca agonists and antagonists with different structures of the brain [1, 2] and the quantification of the role of calcium fluxes in the activity of neuronal tissues.

Ischemic Heart Disease and Calcium Antagonists

While angina of effort, vasospastic angina, and hypertension can be regarded as established indications for calcium antagonists, concerning the efficacy and benefit/risk ratio, all other indications still need more clinical evidence.

In situations of complex physiopathology it is especially necessary to explore in more detail the way in which the patient responds and what type of additional medication gives improved results.

This holds true particularly for the controversy concerning the value of calcium antagonists in the treatment of unstable angina [3]. In this situation patients are treated vigorously with several drugs, among them oral calcium antagonists.

This reflects that multiple mechanisms may coexist, recurring at different times and in different succession. Moreover, the progression from unstable angina to myocardial infarction is somewhat difficult to establish.

Consequently the existing trials have not so much focused on replacing some of the drugs but rather on

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the additional benefit to be gained when calcium antagonists are added to the existing medication. Although much more clinical work is necessary it is hypothesized that Ca antagonists have beneficial effects in those patients whose unstable angina is mainly due to a vasospastic component [4, 5].

However, in severe cases where the patient may have been progressed already to myocardial infarction or in which aggregation is more prominent, Ca antagonists given without a beta-blocker seem to have no or sometimes even detrimental effects [6, 7]. To prove the hypothesis will be most difficult due to varying selection criteria.

Concerning acute myocardial infarction, an improvement of the hemodynamic situation has clearly been demonstrated for nifedipine [11]. However, whether the patient benefits is still controversial [8]. Despite good experimental evidence, an effect of this drug on clinical infarct size is still under debate [8–11].

Moreover, the 6-month mortality after acute myocardial infarction does not show any difference from conventional treatment [8]. However, it has clearly been demonstrated that persisting angina after myocardial infarction (postinfarct angina) is much improved by calcium antagonists [5, 12]. Whether calcium antagonists reduce the incidence of secondary infarction as it has been shown for beta-blockers is still subject of clinical investigations.

Early reinfarction in patients with non-Q-wave myocardial infarction could be prevented in a trial investigating diltiazem [13].

Other Cardiovascular Indications

Pulmonary hypertension is reduced when it is due to hypertensive crisis or hypoxia [14]. The data concerning pulmonary hypertension associated with congenital heart diseases or pulmonary fibrosis are not clearly in favor of any conclusion. The effect on pulmonary hypertension is probably not a direct one but seems to depend indirectly on the improvability of myocardial pump function. If this assumption is correct an effect of calcium antagonists on pulmonary hypertension would require a more or less sufficient myocardium which can react to a reduced afterload with an improved pump function.

An improvement of hemodynamic as well as the clinical situation in patients with hypertrophic cardiomyopathy has been shown for verapamil and nifedipine. The effect is maintained over the observation period of about 1 year [15, 16]. However, in patients with resting obstruction at normal pulmonary arterial wedge pressures nifedipine has been found to be contraindicated [17].

Central Nervous System

Recently neurologic disturbances after cardiac arrest with or without surgery have received more attention. A recently published report shows that nimodipine induces a dramatic improvement by about 50% compared with placebo [18].

There may be a direct effect on the central nervous system, as supported by excellent results, especially with nimodipine in patients with subarachnoid hemorrhage (due to aneurysm rupture) [19–21] and stroke [22]. Both the neurologic outcome and the mortality have been reported to be dramatically improved. As there has been no effective therapy for these conditions these results are very promising. For subarachnoid hemorrhage the results from different trials clearly correspond well. The effect in stroke patients still has to be confirmed by additional clinical trials, which are

The enhancement of the fentanyl effect during anesthesia in humans [23] by nimodipine is, according to animal studies, due to a direct interaction of the drug with the brain opiate receptor and can be reversed by a calcium agonist [2]. Whether this has clinical significance remains to be proven. The same reservation holds true for the reduction of spontaneous seizures as well as overall mortality by nimodipine in rats after alcohol withdrawal [24]. These three preliminary results could, if confirmed, certainly open important therapeutic areas especially because calcium antagonists do not have any sedative effects.

Arteriosclerosis

Experimental evidence for an effect of calcium antagonists on arteriosclerosis [25–27] is also promising. However, one has to keep in mind that the experimental models do not directly resemble human disease. The design of an ongoing trial of nifedipine in humans has been published in 1986 [28]. Results will be available at the earliest in 1989.

Renal Effects

Limited experimental and clinical results show that pretreatment with diltiazem might reduce the failure rate of kidney transplants [29]. Preliminary results indicate a delay of the progres-