Calcium Antagonists as Anti-Atherosclerotic Agents

During the last 10 years, several studies have shown that major calcium blockers including nifedipine, verapamil, diltiazem, and their derivatives exert anti-atherosclerotic effects in rabbits, rats, and monkeys fed high-fat diets.\(^1\)-\(^5\) Treatment of rabbits with nifedipine\(^6\) or verapamil\(^7\) has also been reported to accelerate lesion regression after a period of cholesterol feeding. In initial investigations, drug doses per kilogram of body weight were high,\(^8\)\(^,\)\(^9\)\(^,\)\(^10\) but in subsequent experiments with nifedipine\(^11\) and isradipine,\(^12\) dose schedules were similar to those used clinically. Animal experiments with calcium blockers in high dosages have confirmed the low toxicity of these agents.\(^13\) Suppression of atheromatous lesions has usually occurred in the absence of a reduction in the hypercholesterolemic responses to the atherogenic regimen.\(^1\)-\(^12\) However, in most experiments, detailed analyses of fasting and postprandial lipoprotein levels were not reported. In normcholesterolemic animals with localized mechanical arterial injury, calcium blockers have suppressed the formation of proliferative lesions.\(^14\)-\(^15\) In addition, these drugs have prevented arterial calcinosis induced by vitamin D in the absence of hypocalcemic effects.\(^16\)-\(^17\)

Few authors were unable to demonstrate therapeutic effects of calcium blockers in cholesterol-fed rabbits.\(^19\)-\(^24\) As summarized by Stender et al.,\(^19\) diet-induced atherosclerosis in rabbits is very variable, and standard deviations for measures of atherosclerosis often amount to 40% to 50% of group means. With such variabilities, experiments aimed at demonstrating therapeutic reductions of measures of atherosclerosis by 30% to 40% require group sizes of 24 to 34 animals, with a conventional statistical power of 0.8 (\(\beta=0.2\)).\(^25\)\(^,\)\(^26\) This contrasts with sample sizes of some negative studies in which groups of 12 of fewer animals were used.\(^19\)-\(^22\) For instance, Stender et al.\(^19\) found in the aortas of untreated cholesterol-fed rabbits cholesterol concentrations of 19±11 (SD) \(\mu\)mol/g wet tissue weight. To demonstrate a lack of therapeutic efficacy as reported by others (30% to 40% reductions in treated groups), they should have planned their study with sample sizes two to three times larger than those used.\(^25\)\(^,\)\(^26\) These authors mistakenly interpreted our measurements of cholesterol in aortic tissue as being unduly low although our values were similar to those reported in the literature (47 mg cholesterol per gram protein, or, expressed in the units used by Stender et al., 22 \(\mu\)mol cholesterol per gram wet tissue weight).\(^8\)\(^,\)\(^19\)\(^,\)\(^27\) Naito et al.\(^23\)\(^,\)\(^24\) concluded that nicardipine and diltiazem were ineffective in the suppression of atherosclerosis in cholesterol-fed rabbits. In their experiments, aortic sudanophilic lesion areas were unexpectedly small and differed by a factor of three in identically treated control groups (13.9±13.2 [SD] in one control group vs. 4.4±4.81 [SD] in another). With such a variability, it would be extremely difficult to demonstrate any therapeutic effects. An additional difficulty in performing therapeutic trials with calcium blockers is the low aqueous solubility and variable bioavailability of these drugs. Therefore, it is important to monitor closely the pharmacologic effects in animals given these drugs orally. We believe that in studies in which nifedipine was dissolved in the drinking water containing very low solvent concentrations (0.008% ethanol, 0.0013% polyethylene glycol) it is uncertain how much drug the animals received.\(^20\)\(^,\)\(^21\)\(^,\)\(^22\)

Recent cell culture experiments have suggested some possible mechanisms by which calcium blockers may exert anti-atherosclerotic effects. Stein et al.\(^28\) have shown that verapamil in high concentrations inhibits cholesteryl ester accumulation and cell replication of vascular smooth muscle cultured for more than 1 week in the presence of hypercholesterolemic rabbit plasma (d<1.019 g/ml plasma fraction). The antiproliferative effects of calcium blockers on smooth muscle cells in culture have been reported by others.\(^29\)\(^,\)\(^30\) Etingin and Hajjar\(^31\) have shown that aortic smooth muscle cells cultured from hypercholesterolemic animals are depleted of their cholesteryl ester content by the addition of a submicromolar concentration of nifedipine. This effect appeared to be mediated by the stimulation of cyclic 3\', 5'-adenosine monophosphate (AMP)-dependent lysosomal cholesteryl ester hydrolytic activity, an important reaction of reversed cholesterol transport. In a subsequent study, the same authors obtained aortic biopsies from patients undergoing open heart operations.\(^32\) Patients who had been treated with calcium blockers (diltiazem, nifedipine, verapamil) before operation compared to those who had not, exhibited three times higher cholesteryl ester hydrolytic activities and cyclic AMP levels in their aortic homogenates. Calcium blockers in very small concentrations have also been shown to inhibit chemotaxis and migration of smooth muscle in culture (Boyden chamber experiments).\(^33\) In other studies, calcium blockers have been found to influence lipid uptake by macrophages in culture. Daugherty et al.\(^34\) showed that incorporation of radioactive oleate into cholesteryl esters by rabbit avenolar macrophages in the presence of \(\beta\)-VLDL is suppressed by calcium blockers. Schmitz et al.\(^35\)\(^,\)\(^36\) demonstrated that mouse peritoneal macrophages laden with acetylated LDL are stimulated to secrete lipid-rich lamellar bodies under the influence of nifedipine. Since macrophages are generally not thought to express voltage-dependent (L-type) calcium channels, it appears likely that the drug receptors involved are not L-type channels.\(^37\) Calcium blockers exert multiple effects on a variety of membrane channels, transporters, and exchangers.\(^38\) Although these effects are often ob-
served only with high drug concentrations, it should be noted that unmetabolized lipophilic calcium blockers are apt to accumulate 10- to 100-fold inside of cells. As recently summarized by Zernig, it is possible that low-affinity/high-capacity drug receptor sites for calcium blockers play an important role in mediating some of their pharmacologic effects in vivo. Collectively, cell culture experiments suggest that calcium blockers may influence cellular processes postulated to play an important role in lesion formation.

The experimental evidence suggesting that calcium blockers exert anti-atherosclerotic effects has prompted clinicians to assess the effects of calcium blockers on the progression of arterial disease in humans. Several controlled coronary arteriographic trials have been initiated, and some of these studies have now been completed. In the INTACT study, a placebo-controlled, fully blinded, multicenter trial assessing coronary status by computer-assisted arteriography (CAAS method), patients randomized to treatment with nifedipine exhibited, after a 3-year treatment period, fewer new lesions (occlusion severity approximately 40%) and fewer new complete occlusions compared to untreated controls. In a similar arteriographic trial, Waters et al. at the Montreal Heart Institute concluded that nicardipine treatment for 2 years suppressed the formation of small lesions (<20% obstruction). The INTACT (425 patients) and Montreal trials (383 patients) are the largest controlled arteriographic studies reported to date and the only studies besides the FATS trial (103 patients) that used computer-assisted arteriography. In a smaller third study (113 patients), Loaldi et al. found that nifedipine inhibited the formation of new stenoses as well as the progression of pre-existing narrowings in patients randomized to treatment with nifedipine as opposed to those assigned to treatment with propranolol or isosorbide dinitrate. In coronary arteriographic studies, treatment with calcium blockers appears to have exerted little or no arterial hypotensive effects. Similar to the results from animal experiments, no reduction in total plasma cholesterol was observed. Anatomic studies have suggested that verapamil retards the progression of coronary disease, and a controlled coronary arteriographic trial with verapamil (FIPS) will soon be terminated. Anatomic studies indicate that advanced coronary atherosclerotic lesions may exist without appreciable luminal narrowing. "New" or "small" lesions detected by arteriography may, therefore, not necessarily represent small or new lesions. Suppression of small lesions in arteriographic trials with calcium blockers may represent an important finding. Post-thrombolytic coronary occlusions in patients sustaining acute myocardial infarctions are often not severe, which indicates that moderate occlusions, such as those influenced in the calcium-blocker trials, are not without risk. It is of interest that in a controlled arteriographic trial with aspirin, the rate of myocardial infarction was reduced, although the treatment influenced only new lesions. A clinical study supporting the notion that calcium blockers may influence the formation of new vascular lesions is the report by Gottlieb et al. showing that treatment with nifedipine significantly increased the rate of disease-free saphenous coronary bypass grafts 1 year after their implantation.

In conclusion, current experimental evidence indicates that calcium channel blockers such as nifedipine, verapamil, and diltiazem may suppress the formation of atherosclerotic lesions induced by high cholesterol diets or localized arterial trauma. The mechanisms of action by which these drugs exert their anti-atherosclerotic effects are not completely understood. Although recent controlled clinical studies suggest that calcium blockers may retard the progression of coronary disease, large scale trials will be needed to define the utility of these agents for the treatment of atherosclerosis.

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