Are Calcium Ion Antagonists Effective Anti-Atherogenic Agents?

Organic calcium antagonists (CAs) constitute a large group of structurally and pharmacologically diverse compounds having the common action of reducing the entry of calcium ions into cells. Most are effective in the treatment of cardiocirculatory disorders such as myocardial ischemia, arrhythmias, and hypertension. However, the efficacy of these agents as anti-atherogenic agents remains controversial.

Although many experimental studies have been conducted, the failure to derive a concordant view is in large part due to the lack of comprehensive investigations involving individual CAs. More than a dozen CAs have been studied. However, for the most part, significantly different study protocols have been used, and contrasting conclusions have been drawn. Indeed, in a few instances, the use of similar protocols using the same CA have afforded discrepant conclusions. Interstudy differences in results and conclusions may be attributable to large dissimilarities in dosages of the CA, in the time intervals between the atherogenic stimulus and drug intervention, and in the duration of the treatment. Because of the large number of variables involved in experimental designs and the inherent complexities in the natural history of atherogenesis, it is difficult to reconcile and compare the results of the numerous studies.

Recent reviews include consideration of more than 30 experimental studies performed during the last decade to determine whether CAs possess significant anti-atherogenic activity. The CAs that have received the most attention are nifedipine, verapamil, diltiazem, flunarizine, and isradipine. Nearly all of the studies involving these agents used the cholesterol-fed rabbit model of atherosclerosis. Dosages ranging in size from massive to very small pharmacological quantities recommended for the treatment of angina or hypertension have been used. In the important first study of organic CAs as potential anti-atherogenic agents, nifedipine at a dosage 12-fold greater than the usual clinical therapeutic dosage reduced the development of aortic lesions in cholesterol-fed rabbits. A subsequent study, however, utilizing minimal dosages adjusted to normalize blood pressure in hypertensive, cholesterol-fed rabbits and well within the accepted therapeutic range, reported no effect on atherogenesis.

Isradipine is the CA that has shown the most promise as an anti-atherogenic agent at a dosage below that which reduces blood pressure. Isradipine-treated, cholesterol-fed rabbits developed less aortic atherosclerotic surface involvement ($p<0.03$) and less aortic cholesterol content ($p<0.05$) than an untreated group. It is important to note, however, that in this study the cholesterol diet and drug regimen were begun and continued concurrently.

In addition to the consideration of dosage, a major issue regarding whether CAs effectively suppress atherogenesis requires the definition of the temporal relationship of the induction of the atherogenic stimulus and the drug intervention. Newly formed atheromas are small, fatty, soft lesions that tend to become larger, fibrous, and harder. Correspondingly, as the lesions mature, their histological transformation and changes in chemical composition are such that they become much more intractable to influence by drug intervention. Thus the chronology of the atherogenic stimulus, such as a cholesterol-rich diet and the anti-atherogenic agent, are qualified when assessing anti-atherogenic efficacy. In the typical short-term animal studies in which relatively large doses of the CA were given before, or simultaneously with, the initiation of the cholesterol-enriched diet regimen, most, but not all, of the studies reported some inhibition of lesion development. These conclusions were based on reductions in the total surface area of the atheroma in the aorta and on reductions of aortic cholesterol content. These results are in sharp contrast with those obtained when the atherogenic diet significantly preceded the administration of the CAs. In several studies with this approach, there was scant evidence that even large hypotensive dosages had a suppressive effect. Collectively, these observations support the conclusion that when inhibition of lesion development has been observed, the effect was likely due to inhibition of pathophysiologic processes occurring early in the development of the atheromas. No CA appears to be effective in stopping the progression of atherogenesis once it has advanced beyond the very early stages. Moreover, no CA has totally prevented atheroma formation, regardless of dosage or treatment chronology. Since the early stages of atheroma formation in humans frequently commence and proceed toward maturity well before the second decade of life and the genesis of subsequent lesions begins long before symptoms appear, the value of the available CAs as anti-atherogenic agents appears to be limited.

Few experimental studies reporting the anti-atherogenic activity of CAs have found an effect on either the sharply elevated total serum cholesterol levels of the cholesterol-fed rabbit or on the concentrations of the different lipoprotein classes. This points toward unique mechanism(s) of action, because most of the agents used clinically to suppress atherosclerotic disease share the capability of reducing serum cholesterol. And it is this cholesterol-reducing action that is considered to be a major prerequisite for obtaining a substantial reduction in the develop-
ment of ischemic cardiovascular disease. Although the mechanism(s) underlying the purported anti-atherogenic effects of CAs in the presence of hypercholesterolemia have not been defined, their involvement with several pathogenetic mechanisms have been reported. These effects include the protection of endothelial integrity; modulation of the low density lipoprotein receptor to increased low density lipoprotein binding, internalization, and degradation by smooth muscle cells; reduction in smooth muscle cell proliferation and migration; and reduction in the synthesis of matrix components.6,7,8

There is no published comprehensive clinical information regarding the efficacy of CAs as anti-atherogenic agents. However, the first multicenter clinical study (INTACT) has just been completed. This study was designed to test the effects of nifedipine on the progression of early coronary artery disease including the further development of existing stenosis and the formation of new stenoses and occlusions over a 3-year period. A preliminary report indicated that treated patients developed fewer new lesions (p<0.03). No data regarding the progression of existing lesions were given.9

The preliminary results of a nicardipine clinical trial involving 393 patients with diffuse coronary disease indicates that the progression of early, minimal lesions assessed by repeat arteriography may have been suppressed.10,11 The progression of smaller lesions (≥20% diameter stenosis at first study) was reduced (p<0.05) in the treatment group compared with the placebo group. However, at the end of 2 years, there was no overall difference in the frequency of progression or regression between the nicardipine- and placebo-treated groups on either a per patient or a per lesion basis. It was concluded that although nicardipine had no effect on the more mature, occlusive lesions, the progression of early, minimal lesions was retarded.

Recently a large-cohort, multicenter, 3-year study (MIDAS) was begun. It was designed to compare the effectiveness of isradipine versus hydrochlorothiazide in retarding the rate of progression of atherosclerotic lesions in the carotid arteries of hypertensive subjects.12 Because of the relative high potency of isradipine in suppressing experimental atherosclerosis, this study should yield important results over the next several years.

In summary, there is no definitive answer to the question posed in the title. But several statements can be made, which, taken together, convey current knowledge and permit qualified responses. CAs represent a category of heterogeneous compounds, each having a characteristic set of pharmacological actions, potencies, and side effects. Accordingly, each must be considered individually. Some appear to affect atherogenesis when given at very low dosages and for others, massive dosages are required. A synthesis of the experimental results and the preliminary results of clinical trials suggest that no CA at pharmacological dosages has a major effect on larger, more occlusive atheromas. Considering the fibrosis and mineralization that characterize many of the more mature plaques, little effect would be expected. However, there is some experimental and clinical evidence that nicardipine may suppress the progression of pre-existing small lesions and that nifedipine reduces the rate of new lesion formation. More substantial answers await the evaluation of the data obtained from the clinical trials just completed and the data to be obtained from ongoing studies. It can be stated with certainty, however, that the previous studies do provide strong encouragement and direction for the development of more potent anti-atherogenic agents.

References
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M Overturf

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