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Scientific Update™

Novel L- and T-type Calcium Channel Blockers in Cardiovascular Therapy

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All presently available calcium channel blockers act primarily on the cell membrane L-type calcium channels (long-acting, high-voltage). The T-type calcium channels (transient, low-voltage) were discovered more recently and no selective antagonists have been introduced to clinical practice. Mibefradil is the first of a new class of calcium channel blockers; its unique pharmacologic properties include selective blockade of the T-type calcium channel with a level of voltage-dependent L-type calcium channel inhibition. It is the only clinically tested agent to have such an action. Consequently, mibefradil inhibits sinus node automaticity more than AV conduction or myocardial contractility, leading to decreased heart rate without significant conduction abnormalities or negative inotropic effects. As well, it has a more selective effect on vascular smooth muscle relative to myocardial contractility.

Recent clinical trials confirm the efficacy of mibefradil in hypertension and stable angina. Of great interest, and related to mibefradil's unique action on the T-type channels is whether it will exhibit a beneficial effect in patients with heart failure. This possibility is raised by the fact that normal working myocytes do not express T-type channels, but they are re-expressed as part of the change in the pattern of gene expression seen in the overloaded or failing myocardium. Consistent with this possibility is a recent report indicating that mibefradil is equally effective to cilazapril, an ACE inhibitor, in improving survival in an animal model of heart failure following myocardial infarction.

The Mortality Assessment in Congestive Heart Failure (MACH-1) trial is an ongoing survival evaluation using mibefradil of 2,590 patients with NYHA class 2-4 heart failure and ejection fraction <35%. This trial will conclude in late 1998 and will contribute to elucidate the possible role of this new agent in the management of patients with heart failure.

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T-type Calcium Channels: Table 1

The facts that there are predominantly, if not exclusively, L-type channels in the normal myocardium but that the T-type channels seem to be re-expressed in the abnormal myocardium opens new avenues in the potential applications of this agent. Of great interest, the T-type channels are also present in a diversity of neurohormonal cells and are important in the regulation of the secretion of hormones of great importance to the cardiovascular system, such as renin or aldosterone. Despite a large body of experimental evidence indicating mibefradil has unique pharmacological properties, the important issue is whether these properties translate into meaningful physiological and clinical differences compared with other calcium channel blockers. The findings from a number of experimental and clinical studies are consistent with the postulate that, because of its unique pharmacological properties, mibefradil does result in meaningful clinical differences. Mibefradil produces a consistent decrease in heart rate that is at least comparable to verapamil and exceeds that of other calcium channel blockers. In experimental preparations as well as in humans, its effects on sinus node automaticity exceed those on atrial-ventricular conduction. As well, alone among the calcium channel blockers studied thus far, this new agent prolongs survival in the rat myocardial infarction model.

Hypertension Studies

Results of four placebo-controlled trials utilizing 25 mg to 150 mg of mibefradil once daily in patients with mild to moderate hypertension revealed a dose-dependent decrease in diastolic and systolic blood pressure. In keeping with the long duration of action of this drug, the antihypertensive effects at 24 hour post-dosing were 75-100% of those at peak effect in the recommended dosages of 50 mg and 100 mg.

At least three studies have compared mibefradil with other calcium channel blockers and the results highlight the potential importance of mibefradil's unique pharmacological properties. In a 12-week, randomized, double-blind, forced titration trial of 198 hypertensive patients, mibefradil was compared to diltiazem CD. Following a placebo run-in, patients were randomized to mibefradil, 50 mg once daily, or diltiazem CD, 180 mg once daily. After 4 weeks, mibefradil was increased to 100 mg and diltiazem CD to 360 mg. Mibefradil showed a decline in sitting diastolic blood pressure of 13.0 ± 8 mm Hg versus 9.5 ± 8 mm Hg for diltiazem ($p<0.001$). More mibefradil patients (78% versus 62%, $p<0.02$) achieved a sitting diastolic blood pressure <90 mm Hg or a minimum 10 mm Hg reduction. The heart rate declined an average of 6 beats per minute (bpm) with mibefradil and only 2 bpm with diltiazem. A total of 72% of the patients were controlled with mibefradil versus 51% of the patients with diltiazem ($p=0.002$), although the starting blood pressures

Table 1: Physiological and clinical activities expected from voltage-dependent L-type and specific T-type calcium channel antagonism

Physiological effects	Clinical responses
↓ sinus node automaticity	↓ heart rate
– negative inotropic activity	– hemodynamic deterioration in patients with CHF and LV systolic dysfunction
↓ vascular smooth muscle tone	+ antihypertensive effects
↓ response to pathways modulating growth stimuli	+ anti-anginal effects
	↓ pathological hypertrophy and remodeling

↓ = reduced; – = lack of; + = enhanced

were identical. In terms of side effects, it can be argued that diltiazem is one of the presently available calcium channel blockers that has an excellent side-effect profile. In this trial, there was no significant difference in the overall side-effect profile, although there was a much lower incidence of headaches and substantially lower incidence of edema with mibefradil treatment.

In a study of quite severe hypertensive patients by Dr. R.Y. Lacourciere from Laval University in Quebec, mibefradil was compared to nifedipine GITS. These patients had diastolic blood pressures of 110 to 125 mm Hg going into the study. Patients were titrated to mibefradil 150 mg once daily, versus nifedipine GITS, 90 mg once daily, over a period of 6 weeks. At that time, 20 mg of lisinopril was added if necessary to achieve blood pressure control. A total of 74 patients were entered, of which 71% were randomized, approximately 50% to each group. Only a minority of patients was controlled with a single drug in both groups, as expected in a population of severely hypertensive patients. The study followed office and ambulatory blood pressure monitoring. Mibefradil lowered both measures more significantly than nifedipine, an effect that was seen over the entire 24-hour period.

Anti-ischemic Studies

As well, five placebo-controlled trials have been conducted with mibefradil compared to other calcium channel blockers in chronic stable angina. These studies have shown a consistent increase in the duration of exercise, the time to onset of angina, and the time to 1-mm ST-segment depression during exercise testing over a dose range of 50 mg to 150 mg once daily of mibefradil. Two studies compared mibefradil with other calcium channel blockers. The first compared 100 mg of mibefradil versus 10 mg of amlodipine and showed significantly greater increases with mibefradil in exercise duration, time to onset of angina, and time to 1-mm of ST-segment depression.

A large study by researchers in Israel and the European Investigators Group tested mibefradil in three doses (50, 100, and 150 mg), placebo, or amlodipine 5 mg and 10 mg. There were 60 patients in each group who were treated over a 3-week period, then underwent exercise testing. The primary endpoint in the study was the duration of exercise. Maximal effect was seen with 100 mg of mibefradil, which was significantly better than placebo and amlodipine. In this study, the latter was no better than placebo. As well, mibefradil was substantially better than amlodipine and placebo in time to 1-mm ST-segment depression. It is not clear whether there are differences in coronary flow in patients treated with mibefradil versus other calcium channel blockers; however, superior effects could be explained by more traditional parameters, such as reduction in the heart rate x blood pressure double product. In this study, there was no difference in blood pressure at peak exercise but the heart rate was decreased substantially with mibefradil, while it did not change with amlodipine resulting in a very significant difference in the double product.

Additionally, a 12-week study (mibefradil 100 mg once daily versus diltiazem SR, 120 mg bid) showed a trend to an increased time to 1-mm ST-segment depression for mibefradil (93 ± 88 versus 65 ± 96 sec; p=0.059). Therefore, mibefradil may have enhanced anti-anginal effects as its blockade of L-type and T-type calcium channels may be additive.

Further anti-ischemic effect of mibefradil and cardizem CD will be studied in patients with stable angina in an upcoming trial coordinated by the Clinical Trials Unit at St. Michael's Hospital.

Studies in CHF

The most interesting and intriguing issue related to mibefradil's unique action on the T-type calcium channels is whether it will have a beneficial effect on pathological myocardial growth and remodeling in patients with heart failure. This extremely interesting issue awaits the conclusion in late 1998 of the Mortality Assessment in Congestive Heart Failure (MACH-1) trial. This is an ongoing survival evaluation of 2590 patients with NYHA Class 2-4 failure and ejection fraction of <35%. Of particular promise with respect to this new agent is the experience with ACE inhibitors and beta blockers in heart failure, demonstrating a closer association between prognosis and factors such as neurohormonal activation and its inhibition, alterations in gene expression, or changes in myocardial geometry and composition than to the hemodynamic effects of the drugs.

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Related Reading

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