SMH ST. MICHAEL'S HOSPITAL

Cardiology

UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

XVIII[TH] CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY, AUGUST 25-29, 1996, BIRMINGHAM, UNITED KINGDOM

Heart Rate Lowering Calcium Antagonists in Cardiovascular Disease Management

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The flux of calcium ions into the cytosol of cardiac cells is regulated by two distinct families of calcium channel proteins. One group of these calcium channel proteins regulates calcium ion entry from extracellular space and another allows calcium to enter the cytosol from intracellular stores. Calcium antagonists constitute a group of drugs which can be identified by their ability to selectively inhibit calcium influx through L-type calcium channels (the other type is called T-type) thus, inhibiting vascular and myocardial contraction. Contrasting with this same mechanism of action, these agents belong to different chemical subgroups, for example phenyldihydropyridines (e.g. nifedipine), benzothiazepines (e.g. Diltiazem), and phenylalkylamines (e.g. Verapamil).

Differences in calcium antagonists

Calcium antagonists are functionally heterogeneous with different affinities for various intracellular and extracellular calcium channels, they also differ in their binding to a receptor, based on its functional state. Dr. C. Thuillez from Rouen, France discussed pharmacological distinction of non-dihydropyridine vs dihydropyridine calcium antagonists and the possible implications of these differences in the area of cardioprotection during the XVIIIth Congress of the European Society of Cardiology held in the last week of August, 1996 in Birmingham, United Kingdom.

All calcium antagonists induce vascular relaxation which leads to an increase in coronary blood flow on one hand and a reduction in afterload, and therefore, a decrease in myocardial oxygen consumption, on the other. In addition, negative myocardial inotropic and chronotropic effect, not unlike that seen with beta blockers, can also reduce myocardial oxygen requirements and contribute to the beneficial therapeutic effect, for example in the treatment of stable angina. Thus, all calcium antagonists exert cardioprotective effect in all experimental models of myocardial ischemia or infarction. However, because of the different hemodynamic effects there are important differences between phenyldihydropyridines which exert vasodilating effect without any decrease in

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heart rate or myocardial contraction (and therefore can induce sympathetic stimulation) and the group of benzothiazepines and phenylalkylamines which do not influence the baroreflex stimulation. Based on these considerations, therefore, it is not surprising that all subgroups of calcium antagonists have been shown to be effective in vasospastic angina and in stable angina. However, only Verapamil and Diltiazem have clearly demonstrated efficacy in post myocardial infarction with a decrease in the number of cardiovascular events, including reinfarction and mortality, in patients without heart failure or significant left ventricular dysfunction. Because Verapamil and Diltiazem can induce a significant negative inotropic effect, they should not be used in the presence of heart failure or significant left ventricular dysfunction in the acute setting of myocardial infarction. Recently presented results of the use of Diltiazem in patients with severe chronic heart failure provide evidence for safety and functional efficacy in a non-acute setting.[1]

Safety of diltiazem in cardiomyopathy: DiDi trial

Diltiazem in dilated cardiomyopathy (DiDi) trial assessed whether the therapeutic use of Diltiazem in adjunct to conventional therapy improves transplant indication free survival, hemodynamics, and well being in the general group of idiopathic dilated cardiomyopathy patients. Previous studies with calcium antagonists have not shown improvement in survival, hemodynamics, or clinical complaints in secondary heart failure.[2] However, evidence exists that calcium antagonists may have a beneficial effect in idiopathic dilated cardiomyopathy, including virus induced etiology,[3] alcohol toxicity,[4] microcirculatory abnormalities,[5,6] and impaired calcium cycling.[7,8]

DiDi trial was conducted from March, 1989 to May, 1992 with 186 patients being enrolled from 11 centers in Germany; 94 patients were randomized to placebo and 92 received Diltiazem treatment. Diltiazem treatment began with 30 mg tid on days 1 and 2 and 60 mg tid on days 3 and 4 (patients more than 50 kg also received 90 mg tid on day 5 and afterwards). Any concomitant medication was allowed except for calcium antagonists and beta blockers. Approximately 70% of patients received ACE inhibitors and digitalis and almost 80% received diuretics. No differences were observed in concomitant medications between the placebo and Diltiazem groups and there were no differences with respect to other baseline characteristics such as age, functional status, ECG findings, or hemodynamic data.

After approximately 24 months of follow-up, the survival rate was 80.6% for placebo and 83.3% for Diltiazem patients ($p = 0.78$). Similarly, the transplant listing free survival was higher in the Diltiazem group (85.2%) compared with the placebo group (80.4%), but it did not reach statistical significance ($p = 0.44$). Patient subclassification according to NYHA functional class demonstrated significantly lower transplant listing free survival in class III and IV as compared to classes I and II, regardless of the study medication ($p = 0.0016$, Figure 1). Similarly, survival of patients with LVEF < 30% was significantly worse than those with LVEF > 30% ($p = 0.004$), however, the negative inotropic action of Diltiazem did not increase the event rate in patients with severe left ventricular dysfunction and, if anything, there appeared to be an insignificant benefit (Figure 2).

126 patients finished the 24 month study period on their study medications. In these patients, the longterm hemodynamic course was determined. All hemodynamic parameters, except pulmonary artery pressure at rest, showed significant improvement in the Diltiazem group and a decrease in cardiac size was more pronounced in the Diltiazem group. Only the Diltiazem group demonstrated a significant increase in cardiac index ($p = 0.011$), stroke volume index ($p = 0.003$), arterial pressures ($p = 0.003$), and a reduction in mean pulmonary arterial pressure at comparable workloads and heart rate ($p = 0.007$).

Figure 1: Heart transplant indication-free survival as classified in terms of study medication and NYHA functional class

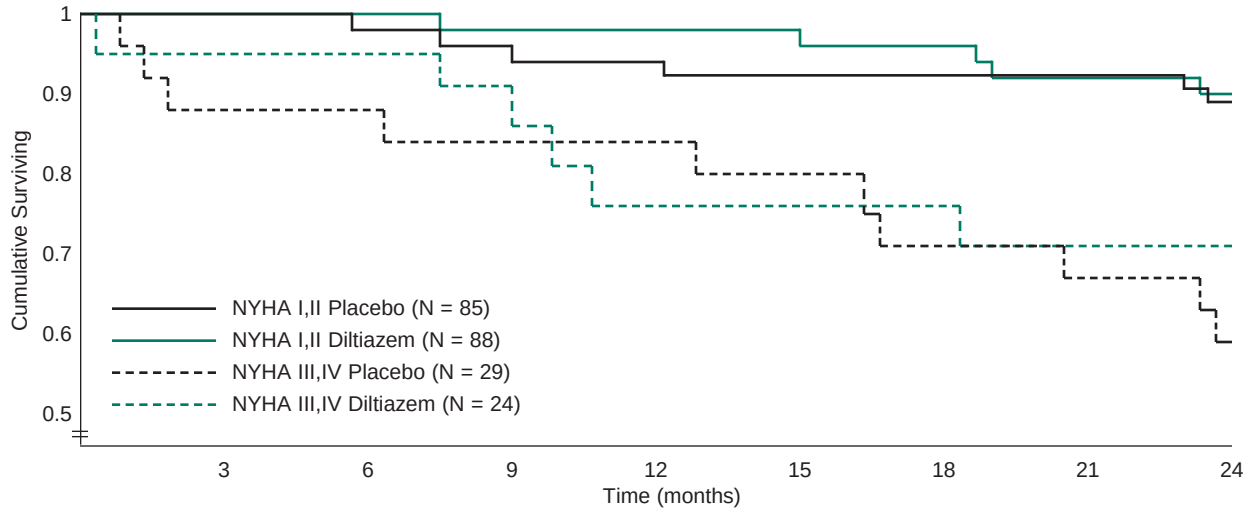
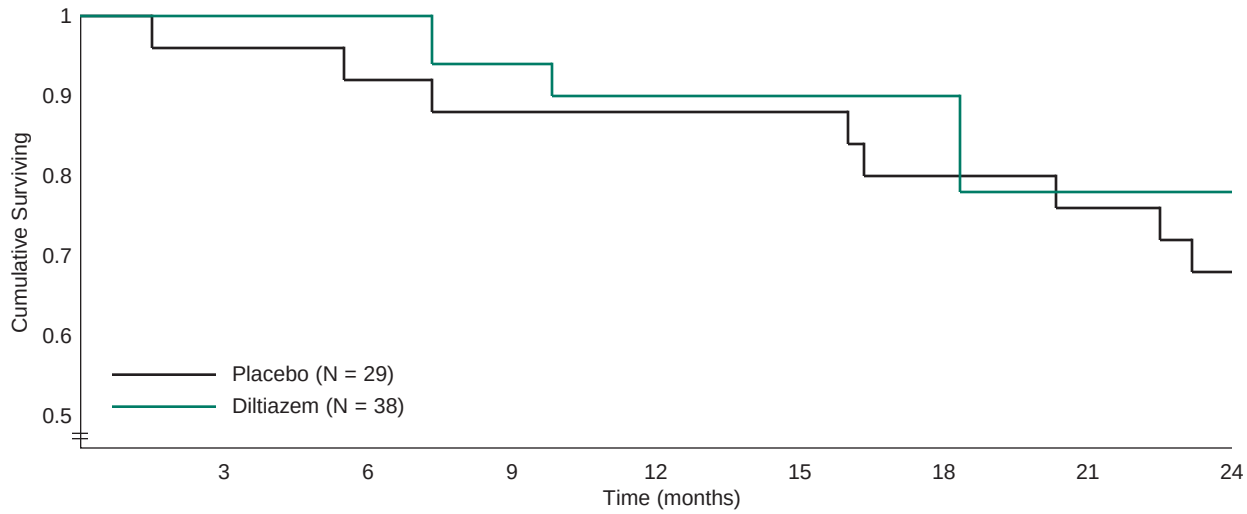


Figure 2: Heart transplant indication-free survival in patients with LVEF ≤ 0.30



Although the norepinephrine plasma levels did not change significantly in either group, there was a trend for fewer PVC's during the 24 hour Holter monitoring in the Diltiazem group (p = 0.086), however, the latter had no effect on the incidence of sudden cardiac deaths. As expected the PQ interval increased in the Diltiazem group, however, no patients developed a second or third degree AV block.

Concomitant with the hemodynamic improvements, the exercise capacity also increased significantly in the Diltiazem group. Interestingly, there was a significant improvement in functional status (Karnofsky's scale and

NYHA) in both groups. However, if the changes in Karnofsky's scale, NYHA functional class, and patient's subjective well being were combined and rated as deteriorated, unchanged, or improved, a significant improvement in the Diltiazem group was demonstrated ($p = 0.01$).

No significant difference in adverse reactions were seen between Diltiazem (16 patients) or placebo (24 patients) groups.

Conclusion

In summary, significant differences exist between various calcium antagonists and their use should be driven by an evidence based approach. Short acting dihydropines may not be safe in patients with coronary artery disease, especially those with acute ischemic syndromes. This potential deleterious effect is likely to be related to neurohormonal activation, increase in heart rate, and increase in myocardial oxygen demand. Heart rate lowering calcium antagonists are safe and beneficial in patients with stable and unstable ischemic syndromes except those with significant left ventricular dysfunction or heart failure. Calcium antagonists appear to be beneficial in the setting of idiopathic dilated cardiomyopathy with beneficial effect possibly related to alterations in neurohoromonal activation, peripheral vasodilatation, relief from microvascular vasospasm, relief of calcium overload, or myocardial protection. The results of DiDi trial, the first published work on the use of calcium antagonists in idiopathic dilated cardiomyopathy, provide evidence that adjunct Diltiazem therapy improves patients' cardiac function, exercise capacity, and subjective status without deleterious effects.

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