

Calcium Channel Blockers in Chronic Heart Failure

The Risks of “Physiologically Rational” Therapy

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A few observations and much reasoning leads to error; many observations and a little reasoning to truth.

—Alexis Carrell

Concerns have been raised about safety of calcium channel blockers in patients with heart failure since their introduction into cardiovascular medicine more than 25 years ago. By inhibiting the influx of calcium into myocardial cells, calcium channel-blocking drugs can depress contractility in both experimental systems and the clinical setting. The magnitude of this effect is enhanced when these drugs are combined with other negative inotropic agents (e.g., β -blockers) or when they are administered to patients with impaired ventricular function.^{1,2} Patients with heart failure are particularly susceptible to the cardiodepressant actions of calcium channel blockers because the failing heart has a profound defect in the delivery of calcium to the contractile proteins.³ In addition, the sympathetic reflexes that normally function to counteract the negative inotropic effects of these drugs are markedly attenuated in chronic heart failure.⁴ As a result, both

See p 1954

hemodynamic and clinical deterioration have been reported during short- and long-term therapy with verapamil, nifedipine, diltiazem, and nicardipine in patients with chronic heart failure.² Some of these events (pulmonary edema and cardiogenic shock) have been life threatening.⁵

Despite concerns raised by these experimental and clinical observations, calcium channel blockers are widely used in patients with impaired cardiac func-

tion. Of the 2,500 patients with mild-to-moderate heart failure enrolled in the Studies of Left Ventricular Dysfunction Trial (SOLVD) sponsored by the National Institutes of Health, 30–35% were treated with a calcium channel blocker in addition to digitalis and diuretics (Dr. B. Pitt and Dr. S. Yusuf on behalf of the SOLVD Investigators, personal communication). Although the calcium channel blockers were generally prescribed for the treatment of the underlying coronary artery disease rather than for heart failure, these agents were used much more frequently in this study than were β -blockers, another class of antianginal drug, which were used in only 5–10%. This fourfold greater use of calcium channel blockers is difficult to explain because β -blockers improve the long-term outcome of patients with left ventricular dysfunction due to ischemic heart disease,⁶ whereas calcium channel blockers have been reported to exert unfavorable effects in this high-risk subset.⁷ Despite these findings, most physicians believe that calcium channel blockers are safer than β -blockers in patients with compromised ventricular function.

Why are calcium channel blockers perceived to be safe in such high-risk patients? Physicians frequently decide to prescribe a drug because of the therapeutic gains it might provide (based on pathophysiological theories) rather than the benefits that it actually delivers (as demonstrated by the results of controlled clinical trials). To the extent that this approach is also used in making decisions about safety, physicians use calcium channel blockers because they believe these drugs should be safe in patients with chronic heart failure. Calcium channel blockers exert potent systemic vasodilator actions, which should offset any adverse effects that these drugs might have on myocardial performance. The cardiodepressant effects of calcium channel blockers should be further minimized by the coronary vasodilator effects of these drugs, which might be expected to alleviate any ventricular dysfunction caused by ischemia. Even if calcium channel blockers were to adversely affect systolic function, these drugs should improve diastolic relaxation, which (if impaired) may contribute importantly to the hemodynamic and clinical abnormalities of many patients with chronic heart failure. Even the ability of calcium channel blockers to

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inhibit the entry of calcium into myocardial cells might be perceived as a beneficial effect because such inhibition could reduce the risk of intracellular calcium overload, an important factor that may mediate the progression of cardiac dysfunction after an acute myocardial injury.⁸

If it is physiologically rational to expect calcium channel blockers to be safe in patients with ventricular dysfunction, how can the adverse hemodynamic and clinical reactions reported in the literature be explained? In some cases, the cardiodepressant effects of these drugs were observed only during the administration of large doses of verapamil, nifedipine, and diltiazem; unfavorable reactions might not have occurred with smaller doses.⁹⁻¹¹ Even if some hemodynamic variables deteriorated after short-term treatment with these drugs, long-term therapy (for weeks or months) might have been well tolerated. (The occurrence of undesirable first-dose hemodynamic effects with converting enzyme inhibitors and β -blockers does not preclude their efficacy and safety during long-term therapy.¹²) Explanations have even been provided for reports of clinical deterioration. According to some investigators, the development of noncardiac leg edema (a common side effect of nifedipine) may have been incorrectly classified as an exacerbation of heart failure. According to others, serious adverse cardiovascular events have occurred only in high-risk patients (those with advanced heart failure)⁵ or during treatment with certain calcium channel blockers (i.e., verapamil and diltiazem).^{7,9} If these hypotheses are valid, hemodynamic and clinical deterioration might not have occurred if only patients with mild-to-moderate heart failure had been treated or if dihydropyridines (e.g., nifedipine and nicaldipine) had been prescribed. To make matters more complicated, all previous episodes of worsening heart failure during long-term therapy with calcium channel blockers have been observed in uncontrolled studies, and it is thus impossible to determine if these adverse events were related to the use of these drugs or to progression of the underlying disease. This uncertainty is heightened in the clinical setting: When given a choice, physicians are more likely to attribute the development of worsening heart failure to the natural history of the disease than to an adverse effect of medications.

Is there any controlled evidence that calcium channel blockers are deleterious to patients with heart failure? Much attention has recently been given to the results of the Multicenter Diltiazem Post-Infarction Trial,⁷ which evaluated the effect of long-term therapy with diltiazem on cardiac death and reinfarction in 2,466 patients who had suffered a recent myocardial infarction. According to the analyses specified in the original protocol, diltiazem exerted neither a favorable nor a detrimental effect in this study. In fact, the ethics committee that closely monitored the trial saw no reason to stop the study prematurely because of either a beneficial or an adverse trend. However, a series of analyses carried

out after the completion of the trial suggested that a subset of patients with radiographic evidence of heart failure on entry into the study experienced a significant increase in mortality when treated with diltiazem. Does such an analysis provide compelling evidence that calcium channel blockers exert clinically important cardiodepressant effects in patients with heart failure? Interestingly, the increase in mortality in heart failure patients treated with diltiazem was not accompanied by an increase in the incidence of worsening heart failure.¹³ When the 490 patients with radiographic pulmonary congestion at the time of randomization were followed for 12–52 months, symptoms of heart failure developed in 17% of the patients treated with diltiazem and 15% of the patients treated with placebo ($p=NS$). Furthermore, if the increased mortality seen with diltiazem had been related to the drug's cardiodepressant effects, we would have expected the mortality risk to be greatest in patients treated with β -blockers, but this was not the case.⁷ Indeed, the analysis that suggested an adverse effect of diltiazem in patients with heart failure was only one of many conducted by the investigators of the study. The other analyses suggested no increased risk in any patient subgroup⁷; two analyses actually suggested a beneficial effect of treatment.^{14,15} To make matters more complicated, some physicians have proposed that any dangers ascribed to diltiazem might not apply to nifedipine, even though several trials have demonstrated a deleterious effect of nifedipine on survival even in patients without heart failure.^{16,17} These uncertainties have led to considerable confusion among physicians regarding the potential hazards of calcium channel blockers in patients with poor ventricular function.

Fortunately, many of these uncertainties are laid to rest by the report by Elkayam et al¹⁸ in this issue of *Circulation*. Their study represents the first controlled trial to demonstrate that calcium channel blockers exert deleterious effects in chronic heart failure. Clinical deterioration occurred more frequently during double-blind treatment with the calcium channel blocker than during the control treatment. These episodes of worsening heart failure were not minor; they were serious enough to require hospitalization or premature discontinuation of therapy. The risk of worsening heart failure was not related to the severity of the disease (at least as assessed by ejection fraction or exercise capacity). Interestingly, the calcium channel blocker used in this trial was not verapamil or diltiazem but nifedipine—a drug that has been perceived by many cardiologists as having minimal cardiodepressant effects, despite hemodynamic evidence to the contrary.^{5,11} Although there was no placebo-treated group in this study,¹⁸ the adverse effects of nifedipine could be clearly discerned because the risk of worsening heart failure during combined therapy with isosorbide dinitrate and nifedipine was greater than during treatment with the nitrate alone. This last observation is

particularly intriguing because we might have expected the addition of an arterial vasodilator (nifedipine) to a venodilator (isosorbide dinitrate) to have produced complementary hemodynamic and clinical benefits. Instead, patients treated with the combination actually fared worse than when treated with either drug alone. These data provide the first compelling evidence that calcium channel blockers are hazardous to patients with heart failure¹⁸ and suggest that the widespread use of these drugs in patients with left ventricular dysfunction (as suggested by the SOLVD data base) may be inappropriate.

What mechanisms might account for the deleterious effects of calcium channel blockers in patients with chronic heart failure? Physicians have long believed that the adverse clinical reactions to these drugs were the direct result of their negative inotropic effects. However, although these drugs can depress cardiac performance, this action does not appear to be responsible for the symptomatic deterioration seen during long-term therapy. Cardiac performance (measured as either cardiac output or ejection fraction) either has remained unchanged or has improved in most patients who have experienced worsening heart failure.^{9,19,20} This pattern of response is particularly characteristic of the second-generation calcium channel blockers (e.g., nisoldipine), which exert minimal cardiodepressant effects but may still exacerbate the symptoms of heart failure.²⁰ Instead, the adverse clinical reactions to calcium channel blockers in chronic heart failure may be related to the activation of endogenous neurohormonal systems (sympathetic nervous system and renin-angiotensin system) that occurs in response to hypotensive effects of these drugs.^{20,21} Although Elkayam et al did not measure neurohormonal variables, it is noteworthy that only the treatments that produced significant hypotensive effects in their study were associated with worsening heart failure. Neurohormonal activation could explain the fluid retention, hypokalemia, and clinical deterioration that have been reported with the use of calcium channel blockers in patients with heart failure.^{19,20,22}; a similar mechanism may also account for the increased risk of worsening heart failure during treatment with other direct-acting vasodilators (including those without negative inotropic effects).²³ Stimulation of the sympathetic nervous system and the renin-angiotensin system could also explain how calcium channel blockers could adversely influence the survival of patients^{7,12,16,17}—an effect that may be neutralized by the concurrent use of specific neurohormonal antagonists.¹⁷

How can the safety of calcium channel-blocking drugs in patients with chronic heart failure be improved? To the extent that neurohormonal activation underlies the clinical deterioration seen with these drugs, physicians could attempt to minimize the adverse effects of presently available calcium channel blockers by combining them with neurohormonal antagonists (especially the converting enzyme inhibitors). No studies are yet available, however, that

demonstrate the validity of this approach, and marked hypotension could occur when two potent hypotensive agents are used together in patients with impaired ventricular function and normal or low blood pressures. Alternatively, new calcium channel blockers could be developed that would exert minimal neurohormonal effects or might even reduce neurohormonal activity in patients with chronic heart failure, possibly as a result of an improvement in baroreceptor sensitivity.²⁴ Preliminary evidence suggests that two investigational calcium channel blockers (felodipine and amlodipine) decrease (rather than increase) plasma levels of norepinephrine and may thereby improve the symptoms and exercise capacity of patients with symptomatic left ventricular dysfunction (Dr. J. Souhrada, personal communication).^{25,26}

Until such agents are available, however, physicians should reevaluate the need for calcium channel blockers in all patients with chronic heart failure, especially if these drugs are being used for nonapproved indications (e.g., postinfarction prophylaxis, silent ischemia, prevention of atherosclerotic plaque progression). The findings of Elkayam et al¹⁸ suggest that the withdrawal of treatment with these drugs may result in significant clinical improvement as well as in a reduction in the need for other therapeutic interventions (e.g., diuretics). Although physicians may believe that it is physiologically reasonable to use calcium channel blockers in patients with chronic heart failure, they should remember a fundamental principle of clinical medicine: Rational approaches to therapy do not necessarily prove to be safe and effective ones.

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