Use of Carvedilol in Chronic Heart Failure: Challenges in Therapeutic Management

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In controlled trials, long-term treatment of patients with chronic heart failure with β-blockers improves symptoms, slows progression of disease, and reduces morbidity and mortality rates. However, in some patients the introduction of therapy can be associated with a period of clinical instability, including risks of fluid retention, hypotension, and bradycardia. Appropriate patient selection and optimization of background therapy can minimize the risk during the introduction of therapy. With vigilance for early signs of clinical deterioration and appropriate adjustment of background medications, the care of most patients exhibiting clinical instability can be successfully managed so the patient is able to continue with the long-term therapy, a prerequisite to realizing beneficial effects. With the initiation of carvedilol, any evidence of fluid retention warrants a prompt increase in the diuretic dosage, and in more pronounced cases the carvedilol dose may need to be reduced or interrupted. In contrast, symptoms of hypotension (most commonly dizziness) generally resolve without intervention, although persistent problems may necessitate adjusting the timing of dose administration or perhaps temporarily reducing the dose of vasodilators or diuretics (the latter with care to avoid fluid retention). Bradycardia should be managed as standard practice would indicate. During long-term treatment, adjustments in β-blocker dosage may be required in the event of an exacerbation of heart failure. Dosages should be adjusted as would be the case with other heart-failure medications, based on the severity of the clinical decompensation, but with care to minimize abrupt changes unless mandated by the patient's condition and to avoid precipitating ischemia or further deterioration. The occurrence of effects such as these does not necessarily indicate that a patient cannot respond favorably to long-term β-blockade, but all require understanding, vigilance, and the availability of medical personnel, especially during the introduction of this therapy.

The rationale for adrenergic antagonism in chronic heart failure is well described.[1,2] The degree of sympathetic activation correlates with disease severity and clinical outcome.[3] Sympathetic neurotransmitters can produce cardiomyocyte dysfunction, producing progressive ventricular dysfunction, and death.[4] Interfering with this cycle alters the natural history of the disease by reducing symptoms, slowing the progression of the underlying disease, and reducing morbidity and mortality rates.[5-7] However, these clinical benefits have not generally been seen during short-term evaluations.[8,9] In fact, during initial antagonism of adrenergic drive, patients may retain salt and water[10,11] and ventricular function can deteriorate.[12] Combined with the pharmacological effects of bradycardia and hypotension, the patient's condition may destabilize during this initiation phase.

Although controlled clinical trials detail the long-term benefits of β-blockers in heart failure, little has been written to describe either the risk profile during the initiation of therapy or the management strategies that will permit patients to achieve target dosages for long-term therapy.[13] These strategies are important because physicians' concerns about these risks are commonly so great that attempts to achieve long-term therapy could be abandoned at the onset of these early side effects. Additionally, long-term therapy could be interrupted permanently in patients who experience transient worsening heart failure after successful titration of β-blocker therapy to target

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dosages, which may not be in the patients' best interest.

This article reviews the basis for the development of clinical instability during the initiation of β-adrenergic blockade in patients with chronic heart failure. Awareness of the long-term benefits of these agents will serve as the impetus to use strategies to permit continued long-term treatment despite the potential for early side effects.

Historical Basis for the Contraindication of β-Blocker Use in Heart Failure

The neurohormonal activation that plays a critical role in the progression of disease in patients with chronic heart failure is typified by the activation of the sympathetic nervous system.[3] This compensatory mechanism serves to preserve organ blood flow acutely, although chronically it contributes to worsening cardiovascular and clinical status. Numerous investigators have documented the risks of producing clinical deterioration acutely when adrenergic blockade is used.[10,11] For example, when patients with chronic heart failure received guanethidine, a ganglionic blocking adrenergic antagonist, over 3 to 17 days, after a gradual reduction in heart rate and blood pressure, these patients exhibited sodium and water retention, followed by increases in venous pressure and body weight.[10] When a similar experiment was conducted with propranolol, a similar shift toward sodium retention was shown over 5 to 10 days, with the development of clinical worsening in several patients.[11] In patients with coronary artery disease, propranolol can produce an acute increase in left ventricular end diastolic pressure and ventricular dilation.[14] In patients with heart failure, acebutolol can produce similar effects.[15] Despite these observations, the clinical use of adrenergic blockade was evaluated in two controlled trials that assessed the clinical and hemodynamic status of patients after 1 month of blinded therapy with either β-blocker or placebo and showed no benefit to β-blocker therapy.[8,9] Finally, in the Beta-blocker Heart Attack Trial, patients with a history of heart failure treated with propranolol were at increased risk of heart failure exacerbations during the first month of therapy.[16] These observations are the basis for the traditional teaching that β-blockers are contraindicated in patients with chronic heart failure.

Rationale for Long-Term Use of β-Blocker Therapy in Heart Failure

Several weaknesses of these early studies limited their applicability. First, the studies used a treatment plan that may have been too short to detect an effect of therapy. Second, the treatment regimens used β-blockers titrated to high doses quickly, without regard for the sensitivity of patients with chronic heart failure to adrenergic withdrawal. These factors would potentially accentuate the adverse pharmacological effects of the agents. Finally, the data stood in contrast to several uncontrolled studies of β-blockade in heart failure showing clinical tolerability and improvement in ventricular function.[17,18]

By the end of the 1980s, several single-center controlled trials of β-blocker therapy showed clinical and hemodynamic benefit during long-term therapy.[1] In fact, every study showed significant improvements in left ventricular function when therapy was continued for a minimum of 3 months,[1] and tolerability was achieved through a gradual increase in dose titration.

The scientific basis for the improvement in ventricular function has been delineated recently. Despite the immediate pharmacological effects of impaired myocardial contractility, adrenergic blockade permits the cardiomyocytes to shift toward a more normal functional state, resulting in improved contractile state.[4,19]

Early multicenter trials of β-blocker therapy showed significant improvements in ventricular function and seemed to indicate a favorable effect on the progression of the disease.[5,6,20] The US Carvedilol Heart Failure Trials Program and the Australia/New Zealand Cooperative group studies with carvedilol showed significant reductions in the risk of disease progression with this agent.[7,21] Patients in the United States Trials Program experienced an improvement in symptoms during therapy.[22,23] These studies are described in greater detail elsewhere in this supplement.[24]

Taken together, both the laboratory and the long-term clinical data support the use of adrenergic blockade in patients with mild-to-moderate heart failure, whereas the short-term data underscore the need for appropriate patient selection and caution during the initiation of these agents.

Patient Selection for β-Blocker Therapy: The Carvedilol Paradigm

The studies showing the effectiveness of carvedilol included patients with mild-to-moderate disease, a low ejection fraction, and who had been optimized on background therapies of diuretics and angiotensin converting enzyme (ACE) inhibitors and in most cases, digoxin. These patients were on stable dosages of diuretics for at least 2 weeks and ACE inhibitors for at least 2 months. Patients had been out of the hospital and had not received intravenous medications for at least 1 month before enrollment. These are the characteristics that patients should ideally have before receiving β-blocker therapy, and they enabled more than 90% of the patients to tolerate the initiation of therapy,[7] the majority of whom in fact did not experience clinical instability during this period.

Challenges During Initiation and Management Strategies

The most prominent pharmacological effects of adrenergic blockade that could adversely affect initiation in patients with chronic heart failure include sodium retention, hypotension, and bradycardia. Although these events seem worrisome, intolerance to carvedilol was observed infrequently when vigilance and appropriate management strategies were used.

Fluid Retention

The frequency of fluid retention during the initiation of therapy with β-blockers has not been specifically described in the literature. Physiological studies showing sodium retention during the initiation of adrenergic antagonism[10,11] would suggest a rational therapeutic intervention, an increase in the dosage of diuretic at the onset of this fluid retention. Generally, the first sign is weight gain. Daily weights can be used to indicate when weight gain is beyond the individual patient's usual variation, which should trigger an increase in the diuretic dosage. Patients should be counseled to contact physicians when their weight increases more than 2 to 3 pounds over a few days, especially if associated with worsening symptoms. If this intervention is used early in the development of fluid retention, the dosage of β-blocker can generally be maintained until resolution of the episode of fluid overload. If fluid retention is marked or the patient is not responding adequately to the intensified diuretic regimen, the β-blocker dose can be temporarily reduced. Because some patients may retain salt and water during the initiation of β-blocker therapy, proper education regarding the importance of enhanced dietary compliance is vital to the successful introduction of therapy.

Crucial to successful introduction of β-blocker therapy is the optimization of the patient's volume status before its initiation. Patients with more advanced disease and with any degree of recognizable fluid overload seem to be at highest risk of developing more marked fluid overload and worsening congestive symptoms during the introduction of anti-adrenergic therapy. In a study of patients with advanced disease, investigators used a strategy of aggressive use of diuretics to eliminate any signs of volume excess before carvedilol initiation.[25] Although 18 of 49 (37%) did develop overt fluid retention (with or without worsening congestive symptoms such as dyspnea) during the initiation of therapy that required an intensified diuretic regimen, all were subsequently titrated to a target carvedilol dose of 25 mg twice a day. The patients who developed fluid retention tended to have a higher right atrial pressure (J.D. Sackner-Bernstein, unpublished observation), emphasizing the need to optimize background therapy before initiation of β-blocker therapy. These data also underscore the higher potential for side effects during introduction of therapy in patients with more advanced disease.

Despite the potential for fluid retention, the risk of developing worsening heart failure during the introduction of carvedilol therapy is low and generally manageable. In fact, in the United States Trials Program, although 6% of the patients experienced worsened heart failure symptoms during the 2-week open-label titration phase, only 1.4% were withdrawn from carvedilol therapy.[7] After patients completed this open-label challenge, they were randomized to receive placebo therapy or continuation of carvedilol, with the attempt to titrate the dosage toward the target. During this double-blind titration phase, the incidence of worsened heart failure symptomatology was 5% in carvedilol-treated patients compared with 4% in the placebo group.[26] During the double-blind maintenance phase, this incidence was lower in the carvedilol-treated patients (16%

vs 21%), as was resultant withdrawal from therapy (1.6% vs 2.3%) over the entire 7.5 months of follow-up.[7]

Hypotensive Effects

Although hypotension during the initiation of carvedilol therapy in patients with heart failure on triple drug therapy would be anticipated, the results of the multicenter trials suggest that the phenomenon is neither severe or refractory. Although dizziness was reported by 33% of patients receiving carvedilol compared with 20% in the placebo group, the dropout rate related to this effect was only 0.4% in the carvedilol group.[7] In the United States Trials Program, 14% of patients experienced dizziness during the 2-week open-label challenge phase, and the incidence of 18% during the up-titration phase was nearly twice that seen in the placebo group. Generally, such episodes do not require intervention. For example, in a series of patients with advanced heart failure, although 11 of 49 (22%) experienced dizziness, only 3 (6%) required adjustment of dosages of background medication and all patients were subsequently titrated to the target dosage.[25]

Successful management of dizziness requires patience. By starting at a low dose and titrating slowly, events are less severe. Dizziness with β-blockers may be viewed as similar to that with ACE inhibitors, the risk is highest in patients with the lowest blood pressure but usually is self-limited and does not preclude successful introduction of therapy. Thus, the primary approach would be to wait patiently until the symptoms resolve, as long as the clinical scenario does not mandate an intervention. If an episode is not self-limited or is more severe, the dosage and timing of administration of ACE inhibitors and vasodilators or diuretics can be adjusted.

One study routinely reduced the dose of ACE inhibitors by 50% before the introduction of bucindolol, with return of the dosage to baseline levels after completing up-titration of bucindolol to target.[27] When rapid-acting ACE inhibitors are used, the adjustment in the dosing interval may be needed to prevent simultaneous peak hypotensive effects of multiple drugs. Long-acting ACE inhibitors may be preferable to avoid abrupt lowering of blood pressure and to enhance the simplicity of the medical regimen, thus improving compliance. Reduction in the diuretic dosage may be considered, but because it carries the risk of salt and water retention over the subsequent days, diuretic reduction should be reserved only for patients who are definitely volume-depleted and without any evidence of volume overload. As with the initiation of ACE-inhibitor therapy, renal perfusion and intrarenal hemodynamics can be affected; therefore, renal function should be monitored during the initiation of β-blocker therapy, especially in patients with abnormal creatinine clearance or renal vascular disease.

Bradycardia

Clinically significant bradycardia with β-blocker therapy in heart failure is less likely than in other cardiovascular disorders, primarily because of the dosing regimen, starting at a low dose and gradually increasing to target. However, there are no uniformly accepted cutoffs for a minimally acceptable resting heart rate for initiation or for continuation of therapy. Multicenter trials designated heart rates of 50 to 60 beats per minute as the minimum to consider a dosage safe to continue treatment in the absence of high-degree heart block.[5-7]

Although the temptation may exist to consider pacemaker therapy to permit safe introduction of carvedilol in patients with relative bradycardia, no controlled trials have established the safety or efficacy of this approach. Nonetheless, in patients receiving long-term carvedilol who develop advanced heart block, pacemaker insertion would seem to be warranted to permit continued β-blocker therapy.

Because of the bradycardic effects of β-blockers and digoxin, it may prove useful to assess digoxin levels, because dose reduction may facilitate reaching the target dose of β-blocker. Carvedilol interacts with digoxin, causing a slight but potentially significant increase in serum digoxin levels. This may be of particular importance in patients with borderline renal function who have reduced clearance of digoxin, or in patients with atrial fibrillation who may be receiving higher dosages of digoxin.[28]

Other Effects

Beta-blockers can produce significant central nervous system effects, manifest as fatigue or depression, which seem to be dose-related. Fatigue

should also be evaluated as a potential cardiovascular effect. Early withdrawal from therapy for this problem may be premature because in general, these side-effects are mild and self-limiting. In some cases, even when the problems persist, patients may prefer to continue on the drug in the hope that their overall well-being will be improved if they continue on therapy long term. Attempts to adjust the carvedilol dosage as well as background therapies may permit continued treatment.

Management of Long-Term Therapy

During Heart Failure Exacerbation

Despite the marked impact of carvedilol on the natural history of chronic heart failure, patients remain at risk for progression of disease. During long-term therapy, patients may experience clinical worsening or exacerbations of heart failure requiring intensified medical therapy and possibly hospital admission. Adjustment in the dosage of carvedilol should be based on the clinical status of the patient and the clinical scenario.

When patients suffer from mild clinical decompensation with mild volume overload from dietary indiscretion, they may not require any adjustment in the carvedilol dosage, only an increase in the diuretic. Often this can be accomplished on an out-patient basis.

At the other extreme, if a patient presents in shock or with severe hypotension, carvedilol should be withheld as should diuretics and ACE inhibitors. Reinitiation of each of these therapies would depend on the response to positive inotropic and/or pressor agents, with introduction of ACE inhibitors and β-blockers withheld until clinical stability is shown after the withdrawal of inotropes and pressors.

When patients present with significant clinical decompensation requiring hospitalization but not necessarily intensive-care management, decisions must be individualized. In general, the dose of β-blocker should be adjusted as would that of an ACE inhibitor. For example, patients with low blood pressure who are markedly volume overloaded may respond to diuretics better if the doses of β-blocker and ACE inhibitor are reduced, but they may not need medication withdrawn. In contrast, when these medications are to be discontinued, the management of the drugs would differ. ACE inhibitors can be abruptly stopped, at least in patients without significant hypertension. In contrast, β-blockers should be withdrawn gradually, with the dosage decreased in weekly intervals if possible, particularly in those with coronary artery disease who may have a rebound increase in angina.

In any of these scenarios, reintroduction of ACE inhibitors and β-blockers should be considered only after the patient is clinically stable and intravenous inotropic therapies have been withdrawn. The introduction of a β-blocker should be delayed until ACE inhibitor therapy is established. As is the case when selecting patients de novo, the time to administer the first dose of β-blocker is after the patient has shown continued clinical stability for several weeks after withdrawal of inotropes and pressors. Caution during this period of reintroduction is crucial. However, it is possible to safely readminister the drugs when patients are selected appropriately.

Initiation of Inotropic Therapy

We have observed a cohort of patients on carvedilol therapy for up to 7 years, some of whom have presented with progressive pump dysfunction leading to consideration of cardiac transplant and initiation of inotropic therapy. Initially, our approach consisted of two phases: first, gradually tapering the dosage of β-blocker to determine whether this alone would improve status, then hospital admission for initiation of inotropic agents. We observed frequent episodes of clinically significant ventricular tachycardia. Subsequently, we changed our approach to continue β-blocker therapy and initiate support simultaneously with phosphodiesterase inhibitors, frequently with a reduction of β-blocker dosage as the clinical scenario requires. In general, patients can be stabilized until transplant with this combination. If there is a lack of response to this combination, the β-blocker can be discontinued gradually.

Conclusions

Carvedilol therapy reduces the progression of disease and improves symptoms in patients with chronic heart failure. The strategies used to introduce β-blocker therapy are similar to those used for ACE inhibitors in patients with chronic heart failure, as are the strategies for management of

carvedilol dosing during long-term use. Selection of patients with mild-to-moderate heart failure who are clinically stable on optimal background medication, together with an understanding of the management of initiation, permits successful introduction of therapy that produces long-term clinical benefit.

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