Inotropic Infusions for Chronic Congestive Heart Failure
Medical Miracles or Misguided Medicinals?
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There are numerous advertisements (1–7) and an occasional article (8–11) advocating intermittent infusions of milrinone or dobutamine for both inpatient and outpatient therapy of chronic heart failure. This development is of concern, because chronic administration of these same agents has been shown to increase mortality rates.

One can hardly open a cardiology journal without encountering advertisements urging physicians to “open new doors” to the treatment of congestive heart failure with a drug that “helps the heart work smarter, not harder™” (1–7). This drug, intravenous milrinone (1–7), is said to increase cardiac index while decreasing pulmonary capillary wedge pressure and systemic vascular resistance, avoid significant change in myocardial oxygen consumption or heart rate, have a rapid hemodynamic response, an easy dosing and administration schedule, a low incidence of side effects and no evidence of tachyphylaxis (1–7).

Perhaps as a tribute to the effectiveness of advertising, to the obsession of hospitals with cost containment, or to the fascination that cardiologists have with hemodynamics, there is also a growing interest in establishing “heart failure clinics” that provide intermittent milrinone or dobutamine infusions therapy of chronic heart failure (8–11). Recommendations are as follows:

“... early, aggressive treatment with IV inotropic therapy has emerged as a strategy for the treatment of advanced heart failure. Recently, interest in the use of these agents in an outpatient setting has increased because of efforts to reduce health care costs. Short term, intermittent IV inotropic therapy can be safely administered to stable outpatients with advanced heart failure, with a goal of improving functional level and avoiding hospitalization” (9).

The intermittent infusion of inotropic drugs in these heart failure clinics is designed to decrease the frequency of hospitalizations—a laudable goal for a condition that is consuming a significant portion of the health care dollar.

The intravenous inotropic agents presently advocated are milrinone and dobutamine. Both milrinone and dobutamine improve the hemodynamics of patients with heart failure (1–17). Dobutamine’s inotropic effect is via its beta agonist action. Dobutamine initiates a cascade that increases adenylate cyclase activity converting adenylate triphosphate (ATP) to cyclic adenylate monophosphate (AMP), the intracellular second messenger of the myocyte that results in the release of calcium from the sacoplasmic reticulum to the contractile proteins—thus its positive inotropic effect. In contrast, milrinone and amrinone increase the intracellular second messenger cyclic AMP by inhibiting phosphodiesterase, the enzyme that breaks down cyclic AMP (18–20).

If positive inotropic effect of the milrinone and dobutamine improve hemodynamics of patients with chronic heart failure, why might one question the practice of intermittent dobutamine or milrinone infusion for chronic heart failure? A review of the published studies of chronic inotropic therapy in patients with chronic heart failure reveals that all chronically administered positive inotropic drugs that increase intracellular cyclic AMP by one mechanism or another have been shown to increase mortality in patients with heart failure (Table 1).

The mortality studies of intravenous infusion of dobutamine are difficult to find because the two reports that suggest a deleterious outcome are published only in abstract form. Table 2 summarizes the control trials with intravenous dobutamine therapy in advanced heart failure that reported mortality.

In the (DICE) study, three patients in the intermittent dobutamine group went on to cardiac transplantation and one patient had to have dobutamine discontinued because of severe ventricular arrhythmias (21). Thus, if mortality, need for cardiac transplantation, and severe arrhythmias are added, 9/19 or 47% of the dobutamine treated group had adverse outcome compared with 3/19 or 16% of the control group (21).

The adverse effect of long term oral inotropic therapy with amrinone in patients with severe heart failure is also not well known, having been published in 1984 (20). In that study, Packer and associates reported that

stroke volume and stroke work indexes increased markedly during the first 48 hours of therapy, returned to pretreatment values in 2 to 10 weeks, but on drug withdrawal deteriorated rapidly to values significantly lower than those

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observed before treatment with amrinone (<.01) despite similar values for left ventricular filling pressure, mean arterial pressure and systemic vascular resistance” (20).

The information on the increased mortality from chronic oral milrinone therapy in patients with chronic congestive heart failure is easier to find, having been published in 1991 in the New England Journal of Medicine (24). The PROMISE research group randomized 1,088 patients with class III and IV heart failure to oral milrinone or placebo. The median period of follow up was 6.1 months. As compared with the placebo, milrinone therapy was associated with a 34% increase in cardiovascular mortality (24). In NYHA class IV patients there was a 53% increase in mortality in the milrinone treated group (24).

If positive inotropic agents improve hemodynamics, why might they be harmful?

Once decreased ventricular systolic function occurs, the patient may be asymptomatic for years, yet there is a progressive and nearly relentless deterioration of ventricular function mediated by as yet incompletely understood stimuli. Neurohormonal activation is thought to be a major contributing factor. An elevated serum catecholamine level is no doubt one of the stimuli, because in patients with chronic heart failure, the higher the serum norepinephrine level the worse the prognosis (29); beta-adrenergic blocking agents not only improve ventricular function (30) but also the prognosis of patients with chronic heart failure due to systolic dysfunction (31,32). It would therefore be logical to conclude that beta stimulation of the chronically failing heart is deleterious. Beta-stimulation increases intracellular cyclic AMP. Other inotropic drugs that increase intracellular cyclic AMP (Table 1) increase mortality and therefore probably contribute to the progressive myocardial deterioration seen in patients with decreased ventricular function.

Katz hypothesized that the decrease in contractile state in heart failure is an important compensatory mechanism that decreases energy use by the failing heart and thereby improves the long-term survival of the cardiac muscle cell (18,20). To quote from Packer and associates,

“Consequently, augmentation of the inotropic state by a variety of drugs . . . could produce a temporary improvement in cardiac contractile performance at the expense of increasing myocardial energy consumption and accelerating death of the myocardial cell. Such a sequence of events may be particularly likely to occur with drugs that enhance inotropy by increasing intracellular levels of cyclic AMP; this nucleotide exerts a direct toxic effect on myocardial cells, which is heightened by agents that stimulate its synthesis (such as catecholamines) or retard its degradation (such as phosphodiesterase inhibitors)” (20).

If a patient with poor ventricular function has a dramatic improvement in hemodynamics with intermittent dobutamine infusion, one should suspect hibernating or stunned myocardium and consider coronary revascularization to improve myocardial perfusion. Infusing dobutamine into a patient who has diffuse coronary disease and heart failure (due in part to hibernating myocardium that is not amenable to revascularization) temporarily increases myocardial contractility, overriding the autoprotective effect of hibernation.

Is intermittent intravenous therapy with the same drug that has been shown to increase mortality when given chronically in an oral form good medicine? Is intermittent therapy with such a drug safe when chronic oral therapy is not? One would think that the burden of proof should be on those advocating intermittent intravenous therapy. This question needs to be addressed by appropriately designed studies.

It is difficult to rationalize the use of a drug intravenously and intermittently when its chronic oral use has clearly been shown to be deleterious. There should be a moratorium on the routine use of intermittent infusion of both milrinone and dobutamine for chronic heart failure until well designed randomized double-blind studies are performed. In such studies, the patients should be fully informed that although inotropic therapy might make them feel better, it also might shorten their life expectancy.

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Table 1. Inotropic Agents that Increase Mortality in Patients with Chronic Heart Failure

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mortality Increase</th>
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<tbody>
<tr>
<td>Amrinone (20)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine (Table 2)</td>
<td></td>
</tr>
<tr>
<td>Enoximone (22)</td>
<td></td>
</tr>
<tr>
<td>Ibopamine (23)</td>
<td></td>
</tr>
<tr>
<td>Milrinone (24–26)</td>
<td></td>
</tr>
<tr>
<td>Vesnarinone (27)</td>
<td></td>
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<tr>
<td>Xamoterol (28)</td>
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</tbody>
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Table 2. Randomized Mortality Trials of Intravenous Dobutamine Therapy in Patients With Severe Heart Failure

<table>
<thead>
<tr>
<th>Author (*)</th>
<th>Dobutamine Mortality</th>
<th>Control Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leier et al (13)</td>
<td>2/15</td>
<td>1/11</td>
</tr>
<tr>
<td>Dies et al (33)</td>
<td>13/31</td>
<td>5/29</td>
</tr>
<tr>
<td>DICE study (21)</td>
<td>5/19</td>
<td>3/19</td>
</tr>
<tr>
<td>Total</td>
<td>20/65</td>
<td>9/59</td>
</tr>
<tr>
<td>Percent</td>
<td>31%</td>
<td>15%</td>
</tr>
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*Reference.
Should prolongation of life be the only goal of therapy? It is argued that a significant number of patients would rather live more comfortably even if their lives are shorter. This is a philosophical issue that has to be answered, one has to know how much shorter; days, weeks, months, years? This has not been studied, but chronic oral administration milrinone shortens patients lives considerably (24).

Another question that is asked concerns the small subgroup of class IV hospital-bound patients who require continuous intravenous inotropes for stability. Should they be considered for home intravenous therapy even if it shortens their life? Using intravenous inotropes in this situation is analogous to placing a balloon pump in a patient with hypotension who does not have a reversible cause. Then the question is “When do you turn it off or take it out?” It should not have been used in the first place.

In my long experience treating patients with severe heart failure due to systolic dysfunction, using the combination of appropriate doses of digoxin, diuretics, ACE-inhibitors, and, at times, a third generation beta-blocker, I have not had to use intravenous inotropic therapy, except for the indications outlined in the paragraph below.

Intravenous inotropic therapy should only be recommended as temporary support for stunned or hibernating myocardium that has been revascularized, or in appropriate hemodynamically unstable patients where there is a specific goal of temporary hemodynamic support until effective therapy can be initiated. Examples include temporary support for an acutely ill patient until one determines if there is a treatable or reversible cause, a patient with possible hibernating myocardium until the patient could be studied and revascularized, a patient with stunned myocardium who has been revascularized or as a bridge to cardiac transplantation.

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REFERENCES