Istaroxime in Heart Failure
New Hope or More Hype*

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Acute decompensated heart failure (ADHF) remains the most common indication for hospitalization in the U.S., accounting for nearly 1 million admissions annually (1). A small minority of patients (approximately 10%) present with a systolic blood pressure below 120 mm Hg on admission (2). These individuals often have evidence of end-organ dysfunction, particularly prerenal azotemia, and generally have progressive heart failure refractory to outpatient therapy. In-hospital mortality averages 7%, whereas 90-day readmission rates approximate 30%. Data from the Acute Decompensated Heart Failure National Registry (ADHERE), identified elevated blood urea nitrogen (≥43 mg/dl) as the best single predictor of in-hospital mortality, followed by low systolic blood pressure (<115 mm Hg) and elevated serum creatinine (≥2.5 mg/dl) (3). Further, the combination of elevated B-type natriuretic peptide and troponin-I can identify patients with a 12-fold increased risk of death during hospitalization (2). Thus, standard measures readily available at the time of hospital admission or shortly thereafter (e.g., vital signs, laboratory values) can provide an important method for assessing in-hospital mortality risk and for basing decisions on the use of hemodynamic monitoring and intravenous vasoactive therapy.

Istaroxime is an inhibitor of the sodium–potassium adenosine triphosphatase pump and also increases sarcoplasmic reticular calcium adenosine triphosphatase isoform 2a (SERCA 2a) activity (8). Evidence that improving SERCA 2a activity may constitute a promising therapeutic strategy for acute heart failure derives from positive results in animal models with either SERCA 2a overexpression or reduction in SERCA 2a activity may constitute a promising therapeutic strategy for acute heart failure (11). The change in dP/dt max during treatment was directly compared in a canine model of chronic ischemic heart failure (4). These findings are not entirely surprising because both dobutamine and milrinone increase intracellular cyclic adenosine monophosphate. Exogenous cardiac stimulation, at a time when the myocardium is significantly energy-depleted, may result in further ischemic or apoptotic damage and lead to the poorer outcomes associated with these agents.

Given the limitations of current inotropic therapy, several new agents are under active investigation for treatment of ADHF, including calcium myosin activators, levosimendan, and istaroxime (5,6). Levosimendan increases calcium myofilament responsiveness by directly affecting contractile proteins to increase contractility without increasing intracellular calcium concentrations (6). Importantly, this agent produces positive inotropic effects without significant increases in myocardial oxygen consumption. Although short-term trials showed levosimendan to be more effective than dobutamine in improving cardiac output and lowering filling pressures, the SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support) study found no difference between levosimendan and dobutamine in 6-month mortality rates (26% vs. 28%) or adverse events such as hypotension and arrhythmias (7). These results have tempered early enthusiasm for this agent.

Istaroxime in Heart Failure (11). The change in dP/dt max during treatment was equivalent between the 2 agents (+51%); however, the peak heart rate was significantly lower with istaroxime. Tissue Doppler imaging studies have shown improvement in myocardial wall thickening, as assessed by peak myocardial early diastolic velocity, by up to 42% (11). Finally, istaroxime has been shown
to improve human SERCA 2a activity in failing human myocytes explanted at the time of heart transplantation (8).

In this issue of the Journal, Gheorghiade et al. (12) describe the first randomized placebo-controlled trial of istaroxime in patients hospitalized with ADHF who underwent hemodynamic monitoring. The HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: A Randomized Control Trial in Patients Hospitalized with Heart Failure) trial was conducted at 3 European sites. Inclusion criteria were left ventricular ejection fraction <35%, systolic blood pressure >90 and <150 mm Hg, and acute heart failure symptoms requiring hospitalization. Patients were excluded for baseline creatinine >3.0 mg/dl or atrial fibrillation. A pulmonary artery catheter was placed within 48 h of hospital admission. Overall, 120 patients were enrolled to receive istaroxime or placebo via a 3:1 (istaroxime:placebo) randomization. Istaroxime was administered at 0.5, 1.0, and 1.5 μg/kg/min for 6 h, and serial hemodynamic assessment was performed. The study cohort was typical of most recent controlled clinical trials with the mean age of 55 ± 11 years. Baseline hemodynamics included a mean blood pressure of 116/70 mm Hg, pulmonary capillary wedge pressure 25 ± 5 mm Hg, and cardiac index of 2.7 l/min/m². Mean left ventricular ejection fraction was 27 ± 6.5%, 98% of patients were classified as New York Heart Association functional class II or III. The cohort was pharmacologically well treated, with over 90% receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 95% receiving a beta-blocker, and 70% receiving spironolactone at study entry. All 3 doses of istaroxime lowered pulmonary capillary wedge pressure, the primary study end point, by 3 to 5 mm Hg compared with placebo. However, cardiac index increased only at the highest dose and was not statistically different at 6 h. Similarly, left ventricular end-diastolic volume decreased significantly (−14.1 ± 26.3 ml) but only at the highest dose. The study confirmed prior animal and clinical studies that showed a significant decline in heart rate and shortening of the QTc interval (−29 to −49 ms) during treatment (13). A favorable lusitropic effect, as assessed by increased mitral deceleration time, occurred only at the highest dose. No acute changes in circulating neurohormones or renal function were noted during the trial. Further, no data were provided about symptomatic improvement or its effect on diuresis. The drug seemed reasonably well tolerated, and no major adverse events occurred during the trial. The investigators correctly conclude that the agent shows early promise in the management of ADHF.

Based on prior animal studies and this clinical trial, there is hope that istaroxime may represent a novel, safe inotropic agent for short-term treatment of ADHF. The drug shows unique mechanisms of action that are independent of increased levels of myocardial cyclic adenosine monophosphate. Unlike dobutamine or milrinone, this agent decreases heart rate, shortens QTc interval, and has no demonstrated pro-arrhythmic effects (11,12). It can acutely lower filling pressures and, at higher doses, improves both cardiac output and lusitropic function. However, istaroxime is far from a proven therapy at this stage. The decreases in pulmonary capillary wedge pressure were quite modest, and the improvement in cardiac output and lusitropic function occurred only at the highest dose studied. Most importantly, the study population did not have evidence for hypotension or end-organ dysfunction and, in fact, had a mean cardiac output of 2.7 l/min/m² before treatment. Current American College of Cardiology guidelines do not recommend inotropic therapy for this “warm and wet” subset of patients with acute decompensated heart failure (14). Finally, this was a very short-term (6 h) dose ranging study performed in patients with mild to moderate symptoms. The investigators correctly conclude that “the fate of istaroxime will depend on its effects on in-hospital and post-discharge clinical outcomes, especially in patients presenting with low cardiac output.”

It is clear to all clinicians who care for ADHF patients that inotropic therapy is most appropriate for a small subset of patients with rapidly deteriorating hemodynamics and progressive end-organ dysfunction (particularly, the cardio-renal syndrome), and as a bridge to heart transplantation or mechanical circulatory support. There is more than a glimpse of hope that istaroxime may prove safer and more effective than currently utilized positive inotropic agents in this challenging heart failure population. Ongoing clinical trials will determine whether the drug lives up to its initial therapeutic promise.

References

7. Mebazaa A. The SURVival of patients with acute heart failure in need of Intra-VEnous inotropic support (SURVIVE) trial (late breaking clinical trials). Paper presented at: American Heart Association Annual Scientific Sessions; November 13–16, 2005; Dallas, TX.


