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EDITORIAL

Istaroxime: Is the Remedy Better than the Disease?

Editorial to: "Chronic Istaroxine Improves Cardiac Function and Heart Rate Variability in Cardiomyopathic Hamsters" by Pietro Lo Giudice et al.

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Acute heart failure (AHF) is a condition with significant morbidity and mortality resulting in more than a million hospitalizations per year in the United States and a similar number in Europe, hence causing a huge financial and public health burden [1–3]. Although almost 40% of AHF patients have relatively preserved left ventricular systolic function, there is also a significant number of cases (10–15%) who require inotropic therapy for severe systolic dysfunction with low cardiac output and/or cardiogenic shock [1, 4].

The currently available inotropic agents, including beta-adrenergic agonists, phosphodiesterase-III inhibitors and calcium sensitizers, although they lead to a short-term hemodynamic and symptomatic improvement, they are followed by a neutral or even adverse long-term outcome [5, 6]. Beta-adrenergic agonists, such as dobutamine, enhance cardiac contractility at the expense of increased myocardial oxygen demand, and therefore may lead to exacerbation of underlying myocardial ischemia, while, at the same time, cause cardiomyocyte calcium overload and increases the risk of arrhythmogenesis, leading to increased mortality [5, 7, 8]. Phosphodiesterase-III inhibitors, on the other hand, may also induce arrhythmias as well as hypotensive episodes and thus adverse clinical outcomes [9, 10]. Finally, levosimendan, a calcium sensitizer with peripheral vasodilating properties, although initially promising [11], failed to show a survival advantage over dobutamine or placebo in large-scale clinical trials [12, 13].

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Two major pathophysiological mechanisms in heart failure are the impaired ventricular emptying, caused by impaired contractility and termed systolic dysfunction, and the defective ventricular filling, caused by compliance abnormality and termed diastolic dysfunction [14]. The novel agent istaroxime seems to respond to both of the above abnormalities by its dual mechanism of action that includes inhibition of the sodium-potassium ATPase and stimulation of the sarcoplasmic reticulum calcium ATPase (SERCA) isoform 2 (SERCA2). The first property induces cytoplasmic calcium accumulation with a positive inotropic response, while the second one leads to rapid clearance of cytoplasmic calcium to sarcoplasmic reticulum, leading to myocardial relaxation and a lucitropic response and at the same time preventing arrythmiogenesis caused by calcium overload [15]. Thus, istaroxime acts as an intracellular calcium modulator, in favor of the contraction–relaxation cycle [14].

Several animal studies have addressed the effects of istaroxime in vivo (Table 1). Sabbah et al. showed that intravenous istaroxime in dogs with advanced heart failure leaded to a dose-dependent improvement in left ventricular geometry and function, increased ejection fraction, reduced volumes, end-diastolic pressures and end-diastolic wall stress, without increasing myocardial oxygen consumption, affecting heart rate or causing de novo arrhythmias [16]. Micheletti et al. showed that intravenous istaroxime improved several echocardiographic contraction and relaxation indices in guinea pigs that had been exposed to 3-month aortic banding [17]. In another study by Mattera et al., a 24-hour intravenous istaroxime infusion at 1, 3, and 4 μg/kg/min to dogs increased left ventricular dP/dtmax and -dP/dtmax, without changing heart rate, blood pressure, or double product or causing arrhythmic events [15]. In the same study, istaroxime was also administered for the first time, orally for 34 weeks, to cardiomyopathic Syrian BIO

Table 1 In vivo studies of istaroxime in heart failure

Study	Subjects	N	Regimen	Main effect
Animal studies				
Mattera et al. [20]	Dogs	7	1, 3, 4 μg/kg/min, 24 h IV	↑ LV dP/dtmax
Mattera et al. [20]	Hamsters	100	30 mg/kg, 34w per os	↑ survival by 32%
Sabbah et al. [21]	Dogs	7	0.5–5.0 μg/kg/min, 1 h IV	↑ LV function and geometry
Micheletti et al. [22]	Guinea pigs	18	0.11 mg/kg/min IV	↑ LV contraction and relaxation
Mattera et al. [23]	Dogs	19	Istaroxime 50 μg/kg bolus + 5 μg/kg/min IV, dobutamine 5–7.5 μg/kg/min IV, milrinone 50 μg/kg bolus + 5 μg/kg/min IV	↑ left ventricular function
Clinical trials data				
Ghali et al. [25]	Chronic stable HF, mean LVEF 27%	18	0.005–5.0 μg/kg/min or placebo 1 h IV	↑ myocardial contractility (at ≥1 μg/kg/min)
Gheorghiade et al. [26] (HORIZON-HF)	Acutely decomp. HF, mean LVEF 27%	120	0.5, 1.0, 1.5 μg/kg/min or placebo 6 h IV	↓ PCWP (all doses), ↑ cardiac index, LV volume, transmitral E wave DT (at 1.5 μg/kg/min)
Shah et al. [28] (HORIZON-HF sub-analysis)	Acutely decomp. HF, mean LVEF 27%	120	0.5, 1.0, 1.5 μg/kg/min or placebo 6 h IV	↓ diastolic stiffness (pressure-volume analysis), ↑ mitral TDI E', ↓ E/E' ratio

IV intravenous, *LV* left ventricular, *HF* heart failure, *LVEF* left ventricular ejection fraction, *PCWP* pulmonary capillary wedge pressure, *DT* deceleration time, *TDI* tissue Doppler imaging

TO.2 hamsters. The drug prolonged survival to 32% of the animals [15]. The same investigators have also shown previously that istaroxime was more effective than dobutamine in improving left ventricular performance in the early (2–3 days) and late (2 weeks) phase of acute myocardial infarction in a canine model [18].

In the present issue of the Journal, this very group of investigators reports further on the long-term effects of oral istaroxime on the same cardiomyopathic hamsters they used before [19]. Compared to animals that received a vehicle, oral istaroxime administered for 16 weeks was followed by an improvement of left ventricular geometry and function. The authors also studied for the first time the effects of the compound on the function of autonomic nervous system and on coronary circulation. It is known that sympathetic activation plays a crucial pathogenetic role in the development and progression of heart failure and markers of its function, such as heart rate variability, represent independent predictors of patients' outcome. According to the analysis of heart rate variability, istaroxime prevented the disturbance of autonomic tone by preserving the parasympathetic activity [19], expanding previous reports showing that istaroxime did not affect heart rate [15, 16]. In addition, an improvement of coronary flow reserve was also documented [19]. These two latter findings are of particular importance given the fact that two main drawbacks of classical inotropes are the detrimental effects of sympathetic activation, including tachycardia and arrhythmogenesis, as well as the myocardial ischemia resulting from the increase of myocardial oxygen demand [5]. Therefore, both drawbacks that may largely be responsible for the negative effects of inotropes on long-term outcome, seem to be adequately addressed by istaroxime at least in the experimental field.

Despite the promising results provided by animal studies, the clinical testing of istaroxime is limited to only two trials, an initial small phase I–II study and a later larger phase II one [20, 21]. In the first study, patients with chronic stable systolic heart failure received 4 sequential 1-hour istaroxime infusions, at doses of 0.005–5.0 μg/kg/min [20]. Istaroxime was effective at doses >1 μg/kg/min and well tolerated at doses of up to 3.33 μg/kg/min. Impedance cardiography showed an increased myocardial contractility, while the hemodynamic effect disappeared over 1–2 hours after discontinuation of the infusion. Istaroxime also shortened QT, while ventricular ectopy was not altered.

The first large phase II clinical trial of istaroxime, the HORIZON (a Phase II Trial to Assess Hemodynamic Effects of Istaroxime in Pts With Worsening HF and Reduced LV Systolic Function), randomized 120 patients with reduced left ventricular systolic function, hospitalized for heart failure, to a 6-h infusion of istaroxime or placebo (3:1), at three different dosing schemes (0.5, 1.0 and 1.5 μg/kg/min), within 48 h of their hospitalization [21].

All three dosing regimens lowered pulmonary capillary wedge pressure, which was the primary end-point of the study, while cardiac index, left ventricular end-diastolic volume and transmitral E wave deceleration time improved only with the highest dose regimen. Interestingly, istaroxime decreased heart rate and increased systolic blood pressure, while it had no effects on neurohormones, renal function or troponin, implying that istaroxime may not bear several of the adverse effects of the current positive inotropic agents. A subsequent analysis of the HORIZON-HF data focused on left ventricular diastolic function, as evaluated by pressure-volume analysis and tissue Doppler imaging of the lateral mitral annulus [22]; istaroxime reduced diastolic stiffness, as shown by the pressure-volume analysis, increased the early diastolic wave tissue Doppler velocity (E') and reduced the E/E' ratio.

The current study by Lo Giudice et al. [19] on one hand fills in a spectrum of animal trials on istaroxime and on the other stresses the lack of adequate clinical testing of this agent, which prevents its potential clinical use in a field in which effective drugs are noticeably missing.

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