**EFFECT OF THE SELECTIVE CARDIAC MYOSIN ACTIVATOR, OMECAMTIV MECARBIL, ON LEFT ATRIAL PERFORMANCE IN HEALTHY MEN**


**BACKGROUND**

Omeamtic mecarbil (formerly known as CK-1827452) is a small molecule designed to improve cardiac function by the novel mechanism of directly activating cardiac myosin. In a dog model of heart failure, intravenous infusion of omeamtic mecarbil increased left ventricular systolic function and cardiac output, with attendant decreases in filling pressures and heart rate. Importantly, these effects on cardiac function did not result in an increase in coronary blood flow or myocardial oxygen demand. As opposed to β-adrenergic receptor agonists and phosphodiesterase inhibitors, which have previously been shown to increase the rate of pressure development (dP/dt) and shorten left ventricular systolic ejection time, omeamtic mecarbil increased systolic function by increasing systolic ejection time without changing dP/dt. Also, in distinction from currently available inotropics, omeamtic mecarbil has no known direct vasoconstricting or vasodilating effects.

In this first-in-humans study, a 6-hour infusion of omeamtic mecarbil was given to healthy men. Consistent with the pre-clinical data, a dose-dependent shortening of the left ventricular systolic ejection time (SET) was noted. In addition, omeamtic mecarbil produced dose-dependent and statistically significant increases in stroke volume, ejection fraction and fractional shortening at 6 hours compared to placebo. Given these improvements in left ventricular systolic function and the similarity of atrial and ventricular cardiac myosin, we hypothesized that omeamtic mecarbil could improve left atrial function. Therefore, we sought to quantify the effects of omeamtic mecarbil on left atrial (LA) performance.

**METHODS**

In this single center, double-blind study, healthy men (n=34 subjects) received a 6 hour double blind infusion each week x 4. Each subject received 3 ascending omeamtic mecarbil doses with a placebo infusion randomized into the treatment sequence. Omeamtic mecarbil was studied at 10 dose rates ranging from 0.005 to 1 mg/kg/hr. Echocardiograms were obtained at baseline, 1, 3, 6, 7, 8, 10, and 24 hrs. From this study, the protocol-specified maximum tolerated dose of omeamtic mecarbil was determined to be 0.5 mg/kg/hr administered for 6 hours. We selected echocardiograms from patients who received both placebo and omeamtic mecarbil at 0.5 mg/kg/hr (n=14-16 for the selected variables) and measured left atrial (LA) and ventricular (LV) volumes as well as Doppler flows blinded to treatment. Left atrial reservoir function was defined as [left atrial end-systolic volume – left atrial end-diastolic volume]/left atrial end-systolic volume] × 100. The least squares mean difference for the change from baseline as compared to placebo was computed and compared between placebo and maximum tolerated dose of OM (0.5 mg/kg/hr) using an ANCOVA analysis based on the following model:

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\text{Change from baseline} = \text{Treatment Groups} + \text{Baseline} + \text{Error}, \text{treating patients as random effect.}
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Analogous to the increase in LV systolic ejection time (SET), omeamtic mecarbil increased the duration of LA contraction (mitral A wave duration). In addition, omeamtic mecarbil increased LA performance as indicated by improvements in LA reservoir function, A velocity, and A’ velocity. No change in HR or E velocity was noted. These improvements in LA performance were associated with increased LV stroke volume as assessed by LVOT velocity time integral (VTI).

**RESULTS**

Echocardiographic parameters taken at 6 hours between treatment group and placebo:

**CONCLUSIONS**

This study is the initial report of improved left atrial performance with omeamtic mecarbil in humans. In previous pre-clinical studies as well as the human studies with omeamtic mecarbil, the most direct evidence of its pharmacologic effect was an increase in LV systolic ejection time. In a similar fashion, the duration of atrial systole (A wave duration) was increased with omeamtic mecarbil. This increase in atrial systole was associated with measures of increased left atrial performance. Although the effect on left atrial performance could be due to improved left ventricular diastolic function, the improvement in A and A’ Doppler velocities support intrinsic improvement in LA contractility. Future clinical studies will measure its effects on left atrial function in heart failure.

**REFERENCES**


