Acute Cardio-Selective Functional Modulation via a Small-Molecule Direct Myosin-Attenuator (MYK-581) Preserves in vivo Diaphragmatic Function in rats: Comparison versus Disopyramide

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a progressive cardiac disease characterized by sarcomeric dysfunction, hyperdynamic contraction, hindered ventricular relaxation/filling, and impaired exercise capacity. Conventional negative inotropes can alleviate the inotropic burden in HCM, but do not improve ventricular filling and have the potential to further decrease exercise capacity due to their off/on-target effects. Recently, a novel small molecule cardiac-myosin attenuator, mavacamten, has been shown to normalize hyper-contractility in patients with obstructive HCM, while improving cardio-pulmonary exercise indices (e.g., Heilner et al., 2019).

This study evaluated and compared the in vivo and ex vivo functional selectivity of MYK-581, a mavacamten analog, with those of disopyramide (DISO), a negative inotrope commonly used to treat HCM patients.

METHODS

In vivo: acute cardiac (left ventricular pressures, LVP) and neuro-muscular force (diaphragm and skeletal muscle contractions) responses to MYK-581 (up to 0.5 mg/kg IV, n = 8) and DISO (up to 10 mg/kg IV, n = 8) were simultaneously evaluated in situ using anesthetized (isoflurane) and mechanically-ventilated Sprague-Dawley rats; diaphragmatic (both intrinsic and phrenic nerve stimulated) and skeletal contractions (stimulated quadriceps) were measured via strain gauges. In another set of rats, cardiac effects were evaluated by echocardiographic and LVP assessments before/after MYK-581 (n = 5) and DISO (n = 5) administration.

In vitro: the functional activity/selectivity of MYK-581 was evaluated both ex vivo via vascular preparations and cardiac (papillary) skinned fiber Ca²⁺-sensitivities assays, as well as in vitro with biochemical assays (ATPase activity) using rat myofibrils (cardiac and diaphragmatic) and myocardial-S1s with actin (14 µM). Tension changes in active and mesenteric artery rings were studied.

RESULTS

MYK-581: selective direct cardiac functional modulation

MYK-581 dose-dependently decreased cardiac myofibrillar ATPase rate (IC̅₀ = 0.42 µM @Ca²⁺ 6.25) showing lower (P < 0.05) potency in diaphragm myofibrils (IC̅₀ = 1.48 µM @Ca²⁺ 6.5) (see Fig. 2A).

Similarly, preferential cardiac activity was seen with clean myosin-S1/actin from cardiac (bovine @0.05 µM, IC̅₀ = 0.32 µM), skeletal (rabbit @0.1 µM, IC̅₀ = 2.23 µM), and smooth muscles (chicken gizzard @0.5 µM, IC̅₀ > 30µM) (see Kawas et al., 2017). In line with these observations, MYK-581 showed negligible effects in aortic (-13.5 ± 2.9% at 30 µM) and mesenteric artery preparations.

In rat permeabilized papillary fibers (Fig 2B), MYK-581 dose-dependently decreased maximal tension, while blunting length-length-dependent activation (LDA) between (2.0 µM) and (long (2.3 µm) sarcomere lengths (SL)) (Green et al., 2016, Anderson et al., 2018, Ma et al., 2019).

MYK-581 decreased indices of systolic function, such as dP/dtmax (-24.9 ± 3.3, n = 13; P < 0.05 vs. PRE) and ejection fraction (EF: -21.5 ± 1.5%, P < 0.05 vs. PRE); reductions in LV systolic function were predicted by plasma exposures. Functional depression with MYK-581 was accompanied by end-diastolic volume increases (EDV: +14.3 ± 3.5%, P < 0.05 vs. PRE), but preserved end-diastolic pressures (EDP: -4.5 ± 6.7%, from 5.7 ± 0.4 to 5.6 ± 0.5 mmHg) suggesting improved ventricular distensibility/compliance (See Fig. 3A) (as supported by a blunted LDA in fibers).

Despite these marked cardiac effects (see Fig. 4), MYK-581 preserved both diaphragmatic (23.7 ± 2.0 to 23.3 ± 2.2 g) and skeletal developed force (14.9 ± 1.4 to 13.9 ± 0.8 g). In contrast, DISO at matched levels of negative inotropy (dP/dtmax: -20.2 ± 2.5, n=13; P < 0.05 vs. PRE; see Fig. 4A) depressed diaphragmatic force (-16 ± 3%, 23.8 ± 1.9 to 19.8 ± 1.2 g, P < 0.05)

CONCLUSIONS

Direct myosin modulation with MYK-581, a mavacamten analog, is characterized in vivo by reductions in systolic function with preserved filling pressures and improved LV compliance.

Unlike disopyramide, MYK-581’s cardiac actions were observed in the setting of preserved diaphragmatic and skeletal force, and were free of vasomotor effects, confirming its biochemical-cardiac-selectivity. This novel pharmacological profile could have salutary effects in patients with HCM and/or impaired ventricular filling presenting with decreased exercise capacity.

REFERENCES

3. HCM and diaphragmatic (e.g., Hagele et al. Biophysics Journal. 71(2): 314 (1996)

DISCLOSURES

All authors, except Rooj SR, are employees and have significant financial interests with Myokard.