

The oral, direct Factor Xa inhibitor rivaroxaban reduced right ventricular pressure increase and hypertrophy without increasing bleeding in a pulmonary artery hypertension model in rats

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Introduction

- ◆ Pulmonary arterial hypertension (PAH) and right heart failure are closely associated with both morbidity and mortality¹
- ◆ PAH is characterized by functional and structural alterations of the pulmonary arterial vasculature with activation of coagulation, local platelet sequestration and thrombosis^{2,3}
- ◆ Anticoagulant therapy is recommended for PAH^{4,5}
- ◆ Rivaroxaban is an oral, direct Factor Xa (FXa) inhibitor that has received a positive CHMP recommendation for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement surgery
- ◆ Rivaroxaban has been demonstrated in four phase III studies to be more effective than enoxaparin in reducing total VTE (composite of any deep vein thrombosis, non-fatal pulmonary embolism or all-cause mortality), without increasing major bleeding, after major orthopaedic surgery⁶⁻⁹

Objective

- ◆ To evaluate whether rivaroxaban could reduce right ventricular pressure increase and hypertrophy in monocrotaline (MCT)-induced PAH in rats

Methods

- ◆ Male Sprague-Dawley rats were randomly assigned to one of four groups (n=7-10 animals per group)
 - Control (no MCT)
 - MCT 60 mg/kg + placebo
 - MCT 60 mg/kg + oral rivaroxaban 3 mg/kg three times daily (tid) for 3 days, followed by 3 mg/kg once daily (od) for 25 days (3-9 mg/kg/day)
 - MCT 60 mg/kg + oral rivaroxaban 10 mg/kg tid for 3 days, followed by 10 mg/kg od for 25 days (10-30 mg/kg/day)
- ◆ Rivaroxaban was administered 4 hours before MCT; MCT was given subcutaneously

- ◆ Twenty-eight days after MCT injection, the following assessments were made:
 - Right ventricular systolic pressure (RVPSys) and right ventricular end-diastolic pressure (RVEDP) were measured via a fluid-filled polyethylene catheter inserted through the right jugular vein into the right ventricle
 - Cardiac output was measured by a transpulmonary thermodilution technique
 - Assessment of right ventricular hypertrophy: the ratio of the right ventricle mass to left ventricle plus septum mass [RV/(LV+S)] was used as an index
 - mRNA levels of brain natriuretic peptide (BNP) in the right ventricle were determined by quantitative real-time polymerase chain reaction
- ◆ Overt bleeding was monitored by daily physical examination (signs of epistaxis and subcutaneous haematoma)

Results

- ◆ Rivaroxaban significantly and dose-dependently reduced the MCT-induced increase in RVPSys compared with MCT + placebo ($p < 0.05$ for 3-9 mg/kg/day and $p < 0.01$ for 10-30 mg/kg/day; Table 1; Figure 1)
- ◆ Rivaroxaban 10-30 mg/kg/day significantly reduced the RVEDP ($p < 0.05$ vs MCT + placebo; Table 1; Figure 2)
- ◆ Rivaroxaban significantly and dose-dependently decreased right ventricular hypertrophy, compared with MCT + placebo ($p < 0.05$, $p < 0.01$ for 3-9 mg/kg/day and 10-30 mg/kg/day, respectively; Table 1; Figure 3)
- ◆ Both doses of rivaroxaban significantly preserved cardiac output (Table 1; Figure 4)
- ◆ Rivaroxaban 10-30 mg/kg/day significantly decreased mRNA levels of BNP in the right ventricle, compared with MCT + placebo ($p < 0.05$; Table 1; Figure 5)
- ◆ No overt bleeding was observed in any study group
- ◆ Two rats in the MCT + placebo group died; there were no deaths in the rivaroxaban groups

Table 1. Effects of rivaroxaban on right ventricular pressure increases, right ventricular hypertrophy, cardiac output and mRNA levels of brain natriuretic peptide in monocrotaline-induced pulmonary artery hypertension model in rats

	Control	MCT + placebo	MCT + rivaroxaban (3-9 mg/kg/day)	MCT + rivaroxaban (10-30 mg/kg/day)
RVPSys (mmHg)	28.6±0.7**	68.3±8.0	54.8±4.4*	44.3±2.8**
RVEDP (mmHg)	2.2±0.2**	5.6±1.0	3.9±0.8	2.9±0.3*
RV/(LV+S)	0.26±0.01**	0.49±0.04	0.41±0.03*	0.33±0.01**
CO (ml/min/100 g body weight)	33.25±1.79*	24.06±2.6	34.78±2.8*	34.99±1.5**
BNP mRNA (arbitrary units)	1,646±165*	14,222±2,983	12,897±2,913	7,383±792*

BNP, brain natriuretic peptide; CO, cardiac output; LV, left ventricle; MCT, monocrotaline; RV, right ventricle; RVEDP, right ventricular end-diastolic pressure; RVPSys, right ventricular systolic pressure; S, septum. Results are mean ± standard error of the mean; * $p < 0.05$, ** $p < 0.01$ vs MCT + placebo (n=7-10).

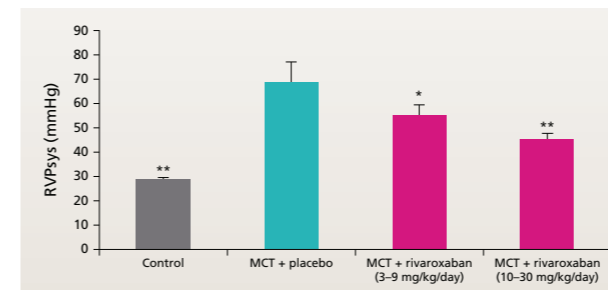


Figure 1. Effects of rivaroxaban (3-9 mg/kg/day and 10-30 mg/kg/day) on right ventricular systolic pressure (RVPSys) in a monocrotaline (MCT)-induced pulmonary artery hypertension model. Results are mean ± standard error of the mean; n=7-10. * $p < 0.05$, ** $p < 0.01$ vs MCT + placebo.

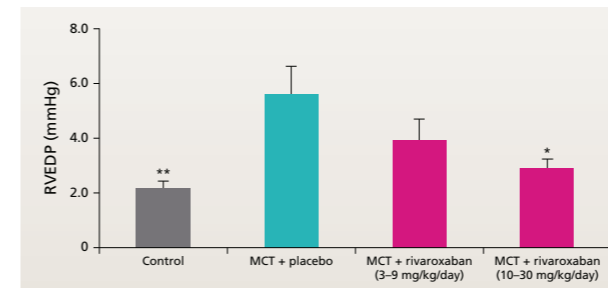


Figure 2. Effects of rivaroxaban (3-9 mg/kg/day and 10-30 mg/kg/day) on right ventricular end-diastolic pressure (RVEDP) in a monocrotaline (MCT)-induced pulmonary artery hypertension model. Results are mean ± standard error of the mean; n=7-10. * $p < 0.05$, ** $p < 0.01$ vs MCT + placebo.

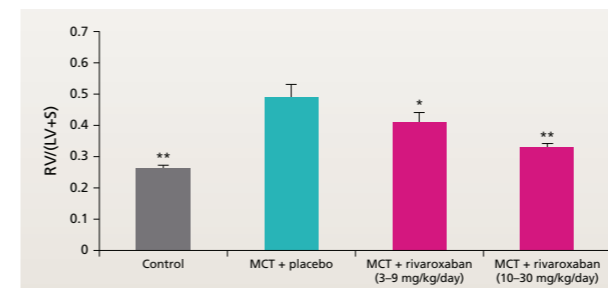


Figure 3. Reduction of right ventricular hypertrophy (mass ratio of right ventricle over left ventricle plus septum: RV/(LV+S)) following rivaroxaban at 3-9 mg/kg/day and 10-30 mg/kg/day in a monocrotaline (MCT)-induced pulmonary artery hypertension model. Results are mean ± standard error of the mean; n=7-10. * $p < 0.05$, ** $p < 0.01$ vs MCT + placebo.

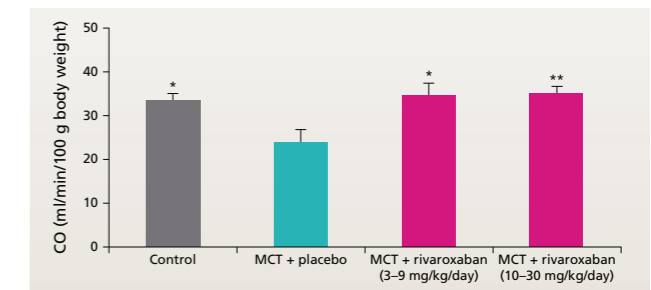


Figure 4. Cardiac output (CO) following rivaroxaban at 3-9 mg/kg/day and 10-30 mg/kg/day in a monocrotaline (MCT)-induced pulmonary artery hypertension model. Results are mean ± standard error of the mean; n=7-10. * $p < 0.05$, ** $p < 0.01$ vs MCT + placebo.

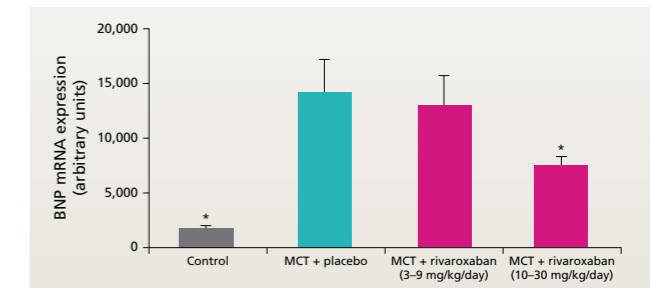


Figure 5. mRNA level of brain natriuretic peptide (BNP) in the right ventricle following rivaroxaban at 3-9 mg/kg/day and 10-30 mg/kg/day in a monocrotaline (MCT)-induced pulmonary artery hypertension model. Results are mean ± standard error of the mean; n=7-10. * $p < 0.05$ vs MCT + placebo.

Conclusions

- ◆ The direct FXa inhibitor rivaroxaban effectively protected against MCT-induced PAH without signs of overt bleeding
- ◆ These findings support the hypothesis that coagulation factors promote the initiation and/or progression of PAH
- ◆ Rivaroxaban could be an effective treatment for patients with primary or secondary PAH

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Disclosure of Conflict of Interest

This study and production of this poster was supported by Bayer HealthCare AG and J&JPRD. Rivaroxaban is in clinical development and not yet licensed.

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