Comparison of the Angiotensin II Type 1-Receptor Antagonist YM358 and the Angiotensin-Converting Enzyme Inhibitor Enalapril in Rats With Cardiac Volume Overload

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ABSTRACT—We evaluated the effects of chronic oral administration of an angiotensin II type 1 (AT1)-receptor antagonist YM358 and an angiotensin converting enzyme inhibitor enalapril on hemodynamics and cardiac hypertrophy in rats with volume overload-induced heart failure. We assessed changes of cardiac hemodynamics and cardiac hypertrophy at 2 and 4 weeks after administration of YM358 (3, 30 mg/kg per day) or enalapril (30 mg/kg per day) in abdominal aortocaval shunt rats. YM358 (30 mg/kg) attenuated increases of left ventricle (LV)/body weight (BW), left atrium (LA)/BW, right ventricle (RV)/BW and heart/BW ratios, but did not affect cardiac hemodynamics in shunt rats. Enalapril also reduced the increased LV/BW and heart/BW ratios together with significant reductions of systolic blood pressure, left ventricular systolic pressure and the first derivative of left ventricular pressure. These data suggest that the effects on attenuation of the development of cardiac hypertrophy are not different for YM358 and enalapril, although the effects on cardiac hemodynamics are different for the same dosages. The attenuating action of YM358 on cardiac hypertrophy was independent of the action on hemodynamics and indicated the direct action of the AT1 receptor on the heart.

Keywords: Cardiac hypertrophy, Heart failure, Aortocaval shunt, Angiotensin II type 1-receptor antagonist, Angiotensin-converting enzyme inhibitor

In patients with heart failure, the sympathetic nervous system and the renin-angiotensin system (RAS) are activated as compensatory mechanisms for maintaining the cardiac function. They have also been postulated to play a key role in cardiac hypertrophy, peripheral vasoconstriction, and sodium and water retention in heart failure. The efficacy of angiotensin converting enzyme (ACE) inhibitors in the treatment of moderate to severe heart failure has been established well (1). Therefore, ACE inhibitors have become the first-choice therapeutic tool for treatment of heart failure. As another tool to inhibit RAS, angiotensin II (Ang II) receptor antagonists have been developed to treat hypertension and heart failure. Recently, several clinical trials on patients with symptomatic heart failure were performed to compare the effects of Ang II-receptor antagonists with those of ACE inhibitors (2–5). The Ang II type 1 (AT1)-receptor antagonist losartan was reported to be superior to captopril in reducing mortality in elderly heart-failure patients in the ELITE (Evaluation of Losartan In The Elderly) Study (2). In the ELITE II Study, however, losartan was not superior to captopril in improving survival, but was significantly better tolerated (5). In the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) pilot study, the AT1-receptor antagonist candesartan was as effective as enalapril in improving exercise tolerance, ventricular function, and quality of life (4). These clinical studies indicated that AT1-receptor antagonists may be as useful as ACE inhibitors in treating patients with heart failure.

YM358 (2,7-diethyl-5-[[2'(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-5H-pyrazolo[1,5-b][1,2,4]triazole potassium salt monohydrate) is a novel nonpeptide competitive AT1-receptor-selective antagonist (6). Moreover, single or repeated administration of YM358 lowered blood pressure in spontaneously hypertensive rats (SHR), stroke-prone SHR, one-kidney, one-clip renal hypertensive rats, and two-kidney, one-clip renal hypertensive rats and dogs (7–9). Al-

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though the efficacy of YM358 for treating hypertension in animal models is well established, little is known about its effectiveness in treatment of heart failure. Therefore, we assessed the effects of YM358 on the development of cardiac hypertrophy and dysfunction in rats with heart failure.

Cardiac overload is an important stimuli that triggers the development of hypertrophy and heart failure in humans (10). Consequently, many models that induce cardiac pressure and volume overload have been developed and characterized. Rats with aortocaval shunt have been proposed as a suitable model for volume overload-induced cardiac hypertrophy and heart failure (11–13). In these rats, plasma renin activity and cardiac renin activity increase quickly and significantly after the shunt surgery (14). In these rats, the AT1-receptor mRNA expression of hypertrophic atria increased by the 4th week after surgery (15). These findings indicate that tissue and/or systemic RAS plays an important role in volume overload-induced cardiac hypertrophy and heart failure and that this model may be suitable for evaluation of effectiveness of ACE inhibitors and AT1-receptor antagonists on the development of cardiac hypertrophy and heart failure. In the present study, we compared the effects of YM358 and enalapril on the time course of changes in cardiac hemodynamics and cardiac hypertrophy in response to volume overload induced by abdominal aortocaval shunt in rats.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 270 – 310 g were obtained from Japan SLC Inc. (Shizuoka). Rats were kept at a controlled room temperature of 22°C, exposed to a 12-h light-dark cycle, and provided with regular rat food and tap water. After an acclimatization period of at least 3 days, they were used in the experiments. The experiments complied with the regulations of the Animal Experimental Ethics Committee of Yamanouchi Pharmaceutical Co., Ltd.

Aortocaval shunt

Under sodium pentobarbital (60 mg/kg, i.p.) anesthesia, shunt surgery was performed using the technique described by Nishikimi et al. (16). Briefly, the shunt was produced using a 20-gauge (diameter, 0.9 mm; length, 38 mm) disposable needle (Terumo Co., Tokyo). The needle punctured the abdominal aorta and advanced into the adjacent inferior vena cava. After temporarily clamping the vessels, the needle was withdrawn and the aortic puncture site was sealed with a drop of cyanoacrylate glue. Animals undergoing sham surgery without puncture of the aorta or the inferior vena cava served as sham-operated rats.

Changes in cardiac hemodynamics and hypertrophy in aortocaval shunt rats

Rats were anesthetized with sodium pentobarbital (60 mg/kg, i.p.), and a polyethylene catheter (PE-50; Clay Adams, Parsippany, NJ, USA) was inserted into the thoracic aorta via the right carotid artery to measure heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Another catheter was inserted into the right jugular vein to measure right ventricular systolic pressure (RVSP) and right ventricular end-diastolic pressure (RVEDP). The catheter was withdrawn to the right atrium to measure the right atrial pressure (RAP). A disposable 22-gauge needle was inserted into the left ventricle (LV) via the diaphragm to measure the left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP). The amplifier receiving the signal from each ventricle was connected by a bridge to a differentiator to register the first derivative of the ventricular pressure from the corresponding side (LV dp/dt max or right ventricle (RV) dp/dt max). Blood pressure data were used to calculate the following values:

- Mean blood pressure (MBP) = DBP + (SBP – DBP) / 3
- Pulse pressure (PP) = SBP – DBP

At the end of each experiment, and while the animals were still under pentobarbital anesthesia, the chest cavity of each was opened. The heart was rapidly excised, and placed into ice-cold saline to remove the blood. To assess cardiac hypertrophy, the LV, left atrium (LA), RV and right atrium (RA) were dissected and weighed at each time point, and lungs were also weighed to evaluate the congestion.

Effects of YM358 and enalapril in aortocaval shunt rats

To assess changes in cardiac hemodynamics and hypertrophy in aortocaval shunt rats, 5 experimental groups were established for both 2- and 4-week administration regimens: sham-operated rats, aortocaval shunt rats administered the vehicle (0.5% methylcellulose solution) as control, aortocaval shunt rats treated with either YM358 (3, 30 mg/kg per day) or enalapril (30 mg/kg per day). As indicated in the tables and figures, each group contained 6 or 7 rats. Oral administration of YM358 or enalapril once a day was started one day after the surgery and then continued every day for either 2 or 4 weeks. At one day after the last administration, measurements of cardiac hemodynamics and cardiac hypertrophy were made as stated above.

Drugs

YM358 was synthesized by the Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Tokyo. Enalapril was obtained from Sigma Chemical Co. (St. Louis, MO, USA). These drugs were suspended in 0.5% methylcellulose solution and administered by oral gavage in a volume of 5 ml/kg.
**Statistical analyses**

All results are expressed as means ± S.E.M. Differences among YM358-administered enalapril-administered and control groups were assessed by one-way ANOVA, followed by Dunnett’s multiple range test. Differences between sham-operated and control groups were evaluated by Student’s t-test. Differences were considered statistically significant at values of *P*<0.05.

**RESULTS**

**Changes in cardiac hemodynamics and hypertrophy at 2 and 4 weeks after aortocaval shunt surgery**

At 2 weeks after the surgery, the aortocaval shunt had not affected the HR, SBP, MBP or DBP, although it increased PP (Table 1). However, LV dp/dmax, LVEDP, RV dp/dmax, RVSP and RAP in aortocaval shunt rats were significantly higher than those of sham-operated rats, but RVEDP of the aortocaval shunt rats was not significantly increased (Fig. 1 and Table 2). The LVSP of aortocaval shunt rats did not increase compared with that of sham-operated rats (Fig. 1). There was no difference in body weight (BW) between shunt and sham-operated rats (Table 3). The LV/BW, RA/BW, RV/BW, RA/BW and heart/BW ratios were significantly higher in aortocaval shunt rats than in sham-operated rats, while the lungs/BW ratio was not affected by the shunt (Table 3).

At 4 weeks after the surgery, the aortocaval shunt did not affect HR, SBP or MBP, but did reduce DBP (Table 1). The relative increases in the LVEDP and RVEDP of aortocaval shunt rats compared with sham-operated rats 4 weeks after the surgery were higher than those 2 weeks after the surgery (Fig. 1 and Table 2). Increases in PP, RVSP and LV dp/dmax in aortocaval shunt rats 4 weeks after the surgery were significant, while increases in RV dp/dmax and RAP in the rats were not significantly affected (Tables 1, 2 and Fig. 1). At 4 weeks after the surgery, LV/BW, LA/BW, RV/BW, RA/BW and heart/BW ratios were significantly increased compared with that in sham-operated rats, and lungs/BW ratio in aortocaval shunt rats was also significantly increased in shunt rats (Table 3).

**Effects of YM358 and enalapril on cardiac hemodynamics in aortocaval shunt rats**

YM358 did not affect any parameter of cardiac hemodynamic variables for 2 weeks of administration (Tables 1, 2 and Fig. 1). YM358 at a dose of 3 mg/kg decreased LVEDP but did not significantly decrease RAP after a 4-week administration (Fig. 1 and Table 2). YM358 at a dose of 30 mg/kg significantly attenuated the increased PP induced by the shunt after a 4-week administration (Table 1). In contrast, enalapril significantly lowered SBP, MBP, and the increased PP after a 2-week administration and also reduced SBP and increase of PP after a 4-week administration.

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**Table 1.** Effects of 2- and 4-week administration with YM358 or enalapril on HR, SBP, DBP, MBP and PP in aortocaval shunt rats

|                | Sham          | Control       | YM358 3 mg/kg | YM358 30 mg/kg | Enalapril 30 mg/kg |
|----------------|---------------|---------------|---------------|---------------|--------------------|
| **HR (beats/min)** |               |               |               |               |                    |
| 2 weeks        | 388 ± 4       | 392 ± 7       | 405 ± 11      | 409 ± 9       | 398 ± 8            |
| 4 weeks        | 380 ± 6       | 383 ± 11      | 392 ± 8       | 385 ± 11      | 381 ± 8            |
| **SBP (mmHg)**  |               |               |               |               |                    |
| 2 weeks        | 144 ± 7       | 145 ± 2       | 148 ± 5       | 142 ± 5       | 127 ± 3*           |
| 4 weeks        | 131 ± 2       | 135 ± 3       | 133 ± 3       | 127 ± 4       | 121 ± 1*           |
| **DBP (mmHg)**  |               |               |               |               |                    |
| 2 weeks        | 107 ± 7       | 99 ± 3        | 102 ± 4       | 101 ± 2       | 90 ± 2             |
| 4 weeks        | 104 ± 1       | 93 ± 2*       | 95 ± 3        | 92 ± 3        | 90 ± 2             |
| **MBP (mmHg)**  |               |               |               |               |                    |
| 2 weeks        | 119 ± 7       | 114 ± 3       | 118 ± 4       | 114 ± 3       | 102 ± 2*           |
| 4 weeks        | 113 ± 2       | 107 ± 2       | 108 ± 3       | 104 ± 3       | 100 ± 2            |
| **PP (mmHg)**   |               |               |               |               |                    |
| 2 weeks        | 37 ± 1        | 47 ± 2*       | 46 ± 1        | 42 ± 2        | 36 ± 1*            |
| 4 weeks        | 27 ± 1        | 42 ± 1*       | 37 ± 1        | 35 ± 1*       | 31 ± 1*            |

Values are means ± S.E.M. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure. *P*<0.05 vs sham-operated rats, **P**<0.05 vs control rats. Groups: sham (2 w, n = 6; 4 w, n = 7); control (2 w, n = 6; 4 w, n = 6); YM358, 3 mg/kg per day (2 w, n = 6; 4 w, n = 7); YM358, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7); enalapril, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7).
Enalapril lowered LVSP after a 2-week administration and the left-side cardiac hemodynamics (LVSP, LV dP/dt_{max} and the increased LVEDP) after a 4-week administration (Fig. 1). Neither 2 nor 4 weeks of administration of enalapril affected the right-side cardiac hemodynamics (Table 2).

**Effects of YM358 and enalapril on cardiac hypertrophy and lung weights in aortocaval shunt rats**

Data are shown in Table 3. YM358 at a dose of 30 mg/kg attenuated the increased LV/BW and heart/BW ratios after a 2-week administration, and it attenuated the increase of LA/BW ratio in addition to increases of LV/BW and heart/BW ratios after a 4-week administration. In contrast, administration of YM358 at a dose of 3 mg/kg for 4 weeks did not significantly attenuate the increased ratio of each cardiac weight to BW in shunt rats. YM358 at a dose of 30 mg/kg per day tended to reduce the increased RV/BW and lungs/BW ratios after a 4-week administration. Both 2- and 4-week administrations of enalapril significantly attenuated the increased LV/BW and heart/BW ratios. Enalapril failed to reduce the increased lungs/BW ratio at all times of measurements.

**DISCUSSION**

The measurements of cardiac hemodynamics and hypertrophy indicated left- and right-side cardiac hypertrophy,
Table 2. Effects of 2- and 4-week administration with YM358 or enalapril on right-side cardiac hemodynamics in aortocaval shunt rats

|                | Sham    | Control | YM358 3 mg/kg | YM358 30 mg/kg | Enalapril 30 mg/kg |
|----------------|---------|---------|---------------|----------------|-------------------|
| RVSP (mmHg)    |         |         |               |                |                   |
| 2 weeks        | 34.2 ± 2.4 | 42.0 ± 1.5* | 41.6 ± 1.4 | 40.4 ± 1.5 | 37.8 ± 2.5 |
| 4 weeks        | 26.8 ± 1.1 | 39.1 ± 1.1* | 37.1 ± 3.1 | 34.1 ± 3.0 | 33.3 ± 1.3 |
| RVEDP (mmHg)   |         |         |               |                |                   |
| 2 weeks        | 0.3 ± 0.2 | 1.3 ± 0.4 | 1.8 ± 0.6 | 1.6 ± 0.6 | 1.7 ± 0.5 |
| 4 weeks        | 0.4 ± 0.3 | 2.5 ± 0.5* | 2.4 ± 0.4 | 1.4 ± 0.6 | 2.0 ± 0.3 |
| RV dP/dtmax (mmHg/s) |         |         |               |                |                   |
| 2 weeks        | 3683 ± 421 | 5433 ± 294* | 5133 ± 276 | 5680 ± 248 | 4960 ± 392 |
| 4 weeks        | 3300 ± 381 | 4420 ± 448 | 4980 ± 604 | 4433 ± 557 | 4083 ± 251 |
| RAP (mmHg)     |         |         |               |                |                   |
| 2 weeks        | 0.1 ± 0.1 | 0.9 ± 0.3* | 1.6 ± 0.5 | 0.4 ± 0.2 | 0.9 ± 0.5 |
| 4 weeks        | 0.3 ± 0.3 | 1.3 ± 0.4 | 0.6 ± 0.2 | 1.1 ± 0.4 | 0.5 ± 0.2 |

Values are means ± S.E.M. RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; RV dP/dtmax, first derivative of right ventricular pressure; RAP, right atrial pressure. *P<0.05 vs sham-operated rats, #P<0.05 vs control rats. Groups: sham (2 w, n = 6; 4 w, n = 7); control (2 w, n = 6; 4 w, n = 6); YM358, 3 mg/kg per day (2 w, n = 6; 4 w, n = 7); YM358, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7); enalapril, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7).

Table 3. Effects of 2- and 4-week administration with YM358 and enalapril on body weight, cardiac weights and lungs weight in aortocaval shunt rats

|              | Sham    | Control | YM358 3 mg/kg | YM358 30 mg/kg | Enalapril 30 mg/kg |
|--------------|---------|---------|---------------|----------------|-------------------|
| BW (g)       |         |         |               |                |                   |
| 2 weeks      | 301 ± 4 | 304 ± 2 | 297 ± 4 | 290 ± 4* | 286 ± 4* |
| 4 weeks      | 319 ± 7 | 320 ± 6 | 321 ± 4 | 309 ± 5 | 314 ± 3 |
| LV/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 1.84 ± 0.03 | 2.32 ± 0.02* | 2.33 ± 0.04 | 2.12 ± 0.05* | 2.07 ± 0.05* |
| 4 weeks      | 1.80 ± 0.01 | 2.53 ± 0.06* | 2.42 ± 0.03 | 2.25 ± 0.05* | 2.13 ± 0.07* |
| LA/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 0.05 ± 0.00 | 0.08 ± 0.00* | 0.09 ± 0.01 | 0.07 ± 0.00 | 0.08 ± 0.00 |
| 4 weeks      | 0.05 ± 0.00 | 0.09 ± 0.00* | 0.08 ± 0.00 | 0.07 ± 0.00* | 0.08 ± 0.00 |
| RV/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 0.44 ± 0.01 | 0.61 ± 0.01* | 0.62 ± 0.02 | 0.62 ± 0.02 | 0.59 ± 0.01 |
| 4 weeks      | 0.45 ± 0.01 | 0.70 ± 0.02* | 0.67 ± 0.03 | 0.63 ± 0.01 | 0.65 ± 0.03 |
| RA/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 0.16 ± 0.01 | 0.28 ± 0.01* | 0.25 ± 0.01 | 0.25 ± 0.01 | 0.25 ± 0.01 |
| 4 weeks      | 0.16 ± 0.01 | 0.30 ± 0.02* | 0.28 ± 0.01 | 0.27 ± 0.01 | 0.27 ± 0.01 |
| Heart/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 2.50 ± 0.03 | 3.28 ± 0.03* | 3.29 ± 0.04 | 3.05 ± 0.08* | 2.99 ± 0.08* |
| 4 weeks      | 2.46 ± 0.02 | 3.63 ± 0.09* | 3.45 ± 0.06 | 3.22 ± 0.07* | 3.11 ± 0.10* |
| Lungs/BW (mg/g) |         |         |               |                |                   |
| 2 weeks      | 3.40 ± 0.09 | 3.53 ± 0.05 | 3.58 ± 0.03 | 3.69 ± 0.05 | 3.67 ± 0.09 |
| 4 weeks      | 3.10 ± 0.04 | 3.60 ± 0.10* | 3.49 ± 0.02 | 3.34 ± 0.05 | 3.65 ± 0.17 |

Values are means ± S.E.M. BW, body weight; LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium. *P<0.05 vs sham-operated rats, #P<0.05 vs control rats. Groups: sham (2 w, n = 6; 4 w, n = 7); control (2 w, n = 6; 4 w, n = 6); YM358, 3 mg/kg per day (2 w, n = 6; 4 w, n = 7); YM358, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7); enalapril, 30 mg/kg per day (2 w, n = 6; 4 w, n = 7).
depression of LV diastolic function, right-side cardiac dysfunction, congestion and lung edema in aortocaval shunt rats, and they deteriorated time-dependently. We also found an enlargement of LV space when cardiac hypertrophy occurred in these rats. Although, in general, significant increase of LVEDP and decrease of LV dp/dt\textsubscript{max} are recognized in heart failure, an increase of LV dp/dt\textsubscript{max} was observed in this study. The increased LV dp/dt\textsubscript{max} in the volume overload model may reflect the compensatory and moderate stage of heart failure. This is supported by clinical studies that indicate chronic volume overload may be tolerated for many years with cardiac performance at normal or near normal levels; meanwhile, LV dysfunction and heart failure develop (17, 18).

Enalapril lowered SBP, MBP and LVSP at 2 weeks and decreased LV dp/dt\textsubscript{max} at 4 weeks after the start of administration. It has been known that the change of LVSP is reflected in the change of SBP or LV dp/dt\textsubscript{max} (19). Therefore, the decrease of SBP after administration of enalapril may explain decreases of LVSP and LV dp/dt\textsubscript{max}, while YM358 did not lower blood pressure in these experiments. Single administration of YM358 lowered blood pressure slightly but significantly in normotensive rats (7). It is unclear whether YM358 acutely lowered blood pressure in these rats because the blood pressure measurement was performed on the day after the last administration (about after 24 h) in this study. YM358 and enalapril decreased the increased LVEDP. Increased LVEDP, RVSP and RAP indicate the increase in pre-load to heart, i.e., pulmonary and systemic congestion, and water and sodium retention in heart failure. It was reported that long-term treatment with enalapril increases urine volume and daily sodium excretion in rats with heart failure (20). The diuretic effect of YM358 shown in our preliminary experiments could also be seen in saline loaded-SHR at a low dose but disappeared at a high dose. Consequently, the decreased LVEDP and RAP after enalapril and YM358 (3 mg/kg) administration may be explained by their diuretic effect in rats.

YM358 decreased the increases of LV/BW, heart/BW and LA/BW ratios. Considering that YM358 did not affect afterload, attenuation of hypertrophy would be induced by the direct effects of YM358 on the AT\textsubscript{1} receptor in myocytes or myofibroblasts. On the other hand, enalapril prevented increases of LV/BW and heart/BW ratios, together with significant reductions of SBP, LVSP and LV dp/dt\textsubscript{max}. Ruzicka et al. (14, 21) reported that enalapril failed to prevent an increase in cardiac Ang II generation and the development of cardiac hypertrophy reflected by volume overload, despite decreasing cardiac load, but in our data, the attenuation of LV hypertrophy was almost the same for YM358 and enalapril in aortocaval shunt rats. YM358 (30 mg/kg) tended to reduce the increased RV/BW and lungs/BW ratios, while enalapril failed to reduce the increased lungs/BW ratio. These data may indicate the different effects of an AT\textsubscript{1}–receptor antagonist and ACE inhibitor on tissue RAS for right-side hypertrophy and pulmonary edema; however, further studies will be necessary to elucidate the mechanism involved.

In summary, YM358 attenuated cardiac hypertrophy independently of afterload in shunt rats, although the effects of YM358 on the development of cardiac hypertrophy in aortocaval shunt rats were the same as those for enalapril. Therefore, YM358 may be a useful tool for preventing the progression of cardiac hypertrophy and remodeling in the case of an undesirable decrease of blood pressure in heart failure.

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