Comparative Antihypertensive Activities of Losartan and HM70186 in Rats with Hepatic Dysfunction

Jae-Hong Choi¹, Sunhee Shin¹, Dongsun Park¹, Jeong Hee Jeon¹, Bong Ho Choi¹, Min-Jung Jang¹, Seong Soo Joo¹, Ki-Wan Oh², Jin Tae Hong², Kwee-Hyun Suh³, and Yun-Bae Kim¹

¹College of Veterinary Medicine and Research Institute of Veterinary Medicine, Chungbuk National University, Cheongju 361-763, Korea, ²College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea, and ³Research Center, Hanmi Pharmaceutical Co., Ltd., Hwaseong 445-813, Korea

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HM70186, a medoxomil ester of EXP3174 which is an active metabolite of angiotensin II receptor blocker losartan, was synthesized, and its antihypertensive efficacy was evaluated in rats with hepatic dysfunction. Male Wistar rats were intraperitoneally injected with 0.5 mL/kg of carbon tetrachloride to cause hepatic injury, and implanted with an osmotic minipump containing angiotensin II (0.4 mg/kg/day) to induce hypertension. After confirmation of both hepatic damage and hypertension, the rats were orally administered losartan or HM70186, and then blood pressure and heart rate were monitored for 24 h. In normal animals, angiotensin II-induced hypertension was lowered by losartan, resulting in an ED₃₀ mmHg of 9.05 mg/kg. HM70186 also immediately decreased the blood pressure in a dose-dependent manner, exhibiting an ED₃₀ mmHg of 0.89 ng/kg (10,000 times the potency observed with losartan). Moreover, HM70186 (3 ng/kg) exerted a strong antihypertensive effect even in rats with hepatic injury, while losartan (10 µg/kg) was ineffective. These results suggest that HM70186 could be a promising candidate for the treatment of hypertension accompanied by hepatic dysfunction.

Key words: Hypertension, Angiotensin II, Losartan, HM70186, Hepatic dysfunction

INTRODUCTION

Hypertension, commonly referred to as “high blood pressure”, is a medical condition in which the blood pressure is chronically elevated, leading to an increased mortality (Eyer, 1975). Persistent hypertension is widely acknowledged as an important circulatory risk factor. There is a strong positive correlation between blood pressure and the likelihood of developing cerebrovascular and cardiovascular diseases, such as cerebral strokes, heart attacks, heart failure and arterial aneurysm and chronic renal failure (Ritz, 2007).

It is known that many pharmacologically important actions, such as contraction of vascular smooth muscle, aldosterone release from the adrenal glands and cell proliferation and hypertrophy of cardiovascular tissues, are mediated by angiotensin II through the interaction with the angiotensin II type 1 receptor (AT₁) (Timmermans et al., 1993; Gridendling et al., 1994). Angiotensin II also acts within the brain to increase sympathetic nervous system activity along with other unfavorable cardiovascular changes. This mechanism is a primary factor for developing experimental models of hypertension (Fink, 1997).

Losartan (2-butyl-4-chloro-1-[(2′-(1H-tetrazol-5-yl)bibenzyl-4-yl)methyl]-1H-imidazole-5-methanol monopotassium) has been widely used as an AT₁-selective, nonpeptide antagonist (Smith et al., 1992), which shows a competitive inhibition with the pressor response to angiotensin II (Wong et al., 1991). In rats, losartan blocked the angiotensin II-induced drinking response and aldosterone release. However, it did not...
lower blood pressure in conscious, normotensive rats because the rennin-angiotensin system plays a minimum role in the control of blood pressure in normotensive rats (Pals et al., 1971). These results suggest that angiotensin II receptor blockade is the primary mechanism for the antihypertensive effects of angiotensin II-receptor blockers (Wong et al., 1990a).

Although it is highly effective with a long-term duration, losartan must be converted into a potent carboxylic acid metabolite, EXP3174 (2-butyl-4-chloro-1-[[2'-[(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylic acid), by CYP450 metabolic enzymes in the liver in order to exert its activity (Fig. 1). Thus, the mean arterial pressure (MAP) of rats with hepatic fibrosis induced by carbon tetrachloride (CCl₄) was not decreased by losartan (Croquet et al., 2002). In addition, losartan exacerbated liver fibrosis and renal dysfunction and increased the mortality of rats with hepatic fibrosis induced by bile duct ligation, although it decreased MAP. Accordingly, it is recommended that losartan should be carefully prescribed for patients with hepatic dysfunction (Merck & Co., Inc., 1995). In light of this, we focused on a chemical derivative with the active metabolite EXP3174 that can be released into blood without undergoing hepatic metabolism by CYP450 enzymes.

In the present study, we compared the antihypertensive effects of losartan and HM70186 (2-butyl-4-chloro-1-[[2'-[(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylic acid medoxomil ester) which is readily converted into EXP3174 by intestinal esterases (Fig. 1). HM70186 was designed to strengthen gastrointestinal absorption and for transformation to EXP3174 without hepatic metabolism. We used a continuous infusion model of angiotensin II for the induction of persistent hypertension (Sarr et al., 2006).

**MATERIALS AND METHODS**

**Materials**

Losartan (originating from DuP753) was synthesized by the Hanmi Pharmaceuticals Research Center (Hwaseong, Korea). HM70186 was synthesized as a medoxomil ester prodrug of EXP3174. EXP3174 is a major metabolite generated after the oral dosing of losartan and is about 30-fold more potent than losartan (DuP753) for inhibiting the pressor effect of angiotensin II. However, unlike losartan, EXP3174 exhibited non-competitive angiotensin II antagonism (Wong et al., 1990b).

**Animals**

Nine week-old male Wistar rats (300-350 g) were purchased from Charles River Co. (Yokohama, Japan), and were housed at the Laboratory Animal Research Center at Chungbuk National University, Korea. The animals (n = 10 per group) were maintained at a constant temperature of 23 ± 1°C, 12-h light/dark cycle and fed with standard rodent chow. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised, 1996), and the protocol was approved by the Institutional Animal Care and Use Committee of Laboratory Animal Research Center, Chungbuk National University.

**Fig. 1.** Plausible metabolic pathways of Losartan and HM70186 to EXP3174, a biologically-active form, in the liver and gastrointestinal (GI) tract, respectively.