[S4-5] [10/19/2001(Fri) 16:30-17:00 /Hall B]

Selective Endothelin-A (ET_A) Receptor Antagonist: Pharmacology and Therapeutic Potential

Jang Yun Lee
Institute of Science & Technology, CheilJedang Corporation, Korea

Since the original report by Yanagisawa et al. on the endothelium-derived 21-residue amino-acid peptide, endothelin (ET) appeared in 1988, compelling evidence indicates that ET plays an important role in the local regulation of smooth muscle and cell growth. The pronounced cardiovascular effects of ETs and the fact that levels of ETs increase in some pathological conditions stimulated continued research into the development of receptor antagonists or actions of ETs. Abbott Laboratories (North Chicago, USA) has an orally active and highly potent ET_A-selective receptor antagonist (A-127722) in clinical development. This presentation will focus on a brief review on the role of ET in cardiovascular diseases, pharmacological characterization of A-127722, and various animal models that demonstrate the pharmacological means of ascertaining the ET receptor antagonists for potential therapeutic utility.

The ETs (ET-1, ET-2 and ET-3) are a family of 21 amino acid peptides. ET is a potent, long-acting vasoconstrictor produced by vascular endothelial cells. ET-1, the main isoform identified in mammalian tissues and fluids, is produced by endotheilial and epithelial cells. The known biological effects of ET-1 are believed to be mediated principally through the ET_A receptor. These include the potent and uniquely sustained vasoconstriction of vascular smooth muscle, positive inotropy of myocardium, and the stimulation of cell proliferation or hypertrophy in vascular smooth muscle cells, cardiac myocytes, and fibroblasts.

In vitro studies in cultured cells have established that A-127722 selectively binds to the ET_A receptor (Table 1), and that A-127722 is a potent competitive inhibitor of ET-1 binding to the ET_A receptor. Studies in cultured human prostate cancer cells and other cultured cells have shown that A-127722 acts as a functional antagonist of ET-1, and these effects have been confirmed in vivo by assessing the effect of A-127722 on the ET-1 induced pressor response in rats (Figure 1). Studies in rats and dogs have suggested that oral A-127722 may be effective in the treatment of congestive heart

failure (CHF) in dogs (Figure 2), pulmonary hypertension in rats, and in the treatment of myocardial infarction (MI) and CHF in rats. There are further suggestions that orally administered A-127722 can prevent arterial restenosis in pigs, and effectively treat hypertension in animals. The effects on the cardiovascular system in dogs are consistent with the proposed effects of A-127722, with dose-related reductions in central venous pressure and left ventricular end-diastolic pressure; no effects are observed on electrocardiograms.

Pharmacokinetic measurements in rats, dogs, and monkeys have given a mean plasma elimination half-time of 1.6~3.5 hours, a bioavailability of 22~35% and observed peak plasma concentration within one hour of dosing (Table 2). Multiple dosing studies have suggested that an induction of metabolizing enzymes or decreased gastrointestinal absorption might contribute to lower plasma levels of A-127722 after chronic administration. A-127722 appears to be metabolized by both oxidative (N-butylation and O-demethylation) and conjugative (glucuronidation) mechanisms, and, in the rat and dog, there is biliary excretion of the glucuronide, hydrolysis to the aglycone, and primary elimination of the parent compound via the feces.

There is a low order of acute toxicity in rodents, and A-127722 is nonmutagenic. Subchronic toxicity studies (1-3 months) in dogs and rats suggested that the liver, and to a lesser extent the kidney, were targets of A-127722; there were also irreversible histologic changes in the rat testis, although the incidence was low and only a few seminiferous tubules were affected. Species-specific, largely reversible; hematologic changes have also been observed in animals treated with A-127722.

TABLE 1. ***Binding properties (Ki) in human ET and ET receptors expressed in CHO cells of A-127722 and other ET antagonists of interest***

Compound	hET_A Ki	hET_B Ki	Reference
	nM	*nM*	
A-127722	0.069	139	
PD 156707	0.17	134	(Reynolds *et al.*, 1995)
SB 209670	0.4	18	(Ohlstein *et al.*, 1994b)
FR 139317	1.0	7,300	(Sogabe *et al.*, 1993)
Ro 47-0203	6.5	343	(Clozel *et al.*, 1994)
BMS-182874	48	>50,000	(Webb *et al.*, 1995)

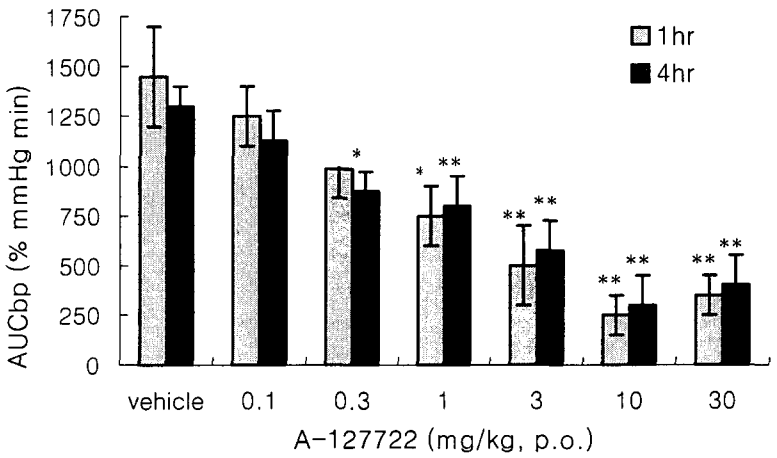

Fig. 1. Dose-response data for the *in vivo* antagonism in conscious rats of ET-1-induced (0.3 nmol/kg i.v. bolus) increases in arterial blood pressure by A-127722 given by gavage. Blood pressure responses to exogenous ET-1 were determined at 1 and 4 hr after dosing (n=8/group)/ AUCbp calculations were made to account for the unique time element of the ET-induced pressure response *in vivo*. *P<.05, ** P<.001

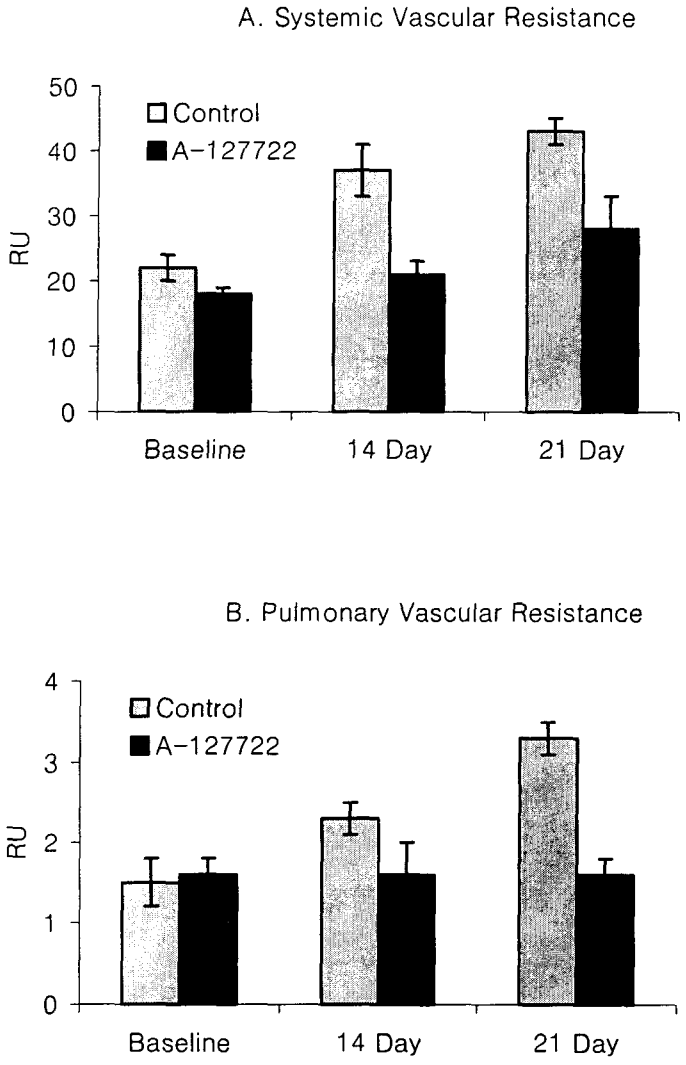

Fig. 2. A-127722 (5mg/kg, p.o., b.i.d.) prevents the marked rise in systemic (A) and pulmonary (B) vascular resistance (RU-resistance units) normally observed with rapid ventricular pacing-induced CHF in the dog.

TABLE 2. Pharmacokinetic comparison of A-127722 in rat, dog and monkey

A- 127722 was administered at 5 mg/kg i.v. and p.o. in each species.

Species	$t_{1/2}$ i.v.	Vc	CLp	Cmax	F
	hr	*l/kg*	*l/hr/kg*	*μg/ml*	%
Rat	3.5	0.26	0.72	1.10	35.4
Dog	1.6	0.13	0.68	4.67	43.7
Monkey	2.5	0.09	0.73	0.32	21.7

Abbreviations: $t_{1/2}$, plasma elimination half-life; Vc, apparent volume of distribution; CLp, plasma clearance; Cmax, maximum plasma concentration achieved after p.o. dosing; F(%), apparent bioavailability.