blinded placebo-controlled study. Participants received single oral tablet of DA-8159 (12.5 to 300 mg) or placebo. Adverse effects and pharmacokinetic parameters were monitored during experiments. DA-8159 was well tolerated and the frequency of adverse events was dose-related. The most common side effects were headache and facial flushing, which are related with inhibition of PDE5. Mean plasma concentrations of DA-8159, maximum concentration (Cmax), and area under the concentration-time curve from time 0 to the time of the last detectable concentration (AUCo-tldc) increased with increasing dose, with the time to the peak concentration in plasma occurring at 1.17 to 1.92 hours postdosing. Plasma elimination half-life (t1/2) ranged from 7.3 to 12.1 hours with an average of 10 hours. This study indicates DA-8159 is safe and well tolerated after single oral dose in healthy males up to 300 mg without severe adverse events and warrants further clinical investigation.

[PA1-21] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Evaluation of electroretinogram and retinal histopathology in rabbits administered DA-8159, a selective PDE 5 inhibitor

Kang KyungKoo°, Ahn GookJun, Sohn YongSung, Shim HyunJoo, Ahn ByoungOk, Kim WonBae, Cho HoKyun

Dong-A Pharmaceutical Research Institute, Department of ophalmology, Chung-Ang University Medical School

DA-8159, a selective inhibitor of phosphodiesterase type 5 (PDE5; IC_{50} 5ng/ml), is being developed as a new treatment for erectile dysfunction. Since DA-8159 has been shown to inhibit PDE6 enzyme (IC_{50} 53ng/ml), we evaluated the effect of DA-8159 on electroretinogram (ERG) and retinal histopathology in rabbits. The effect of oral DA-8159 (5 to 30mg/kg) on ERG recordings was investigated at pre-treatment, 1 and 5 hrs after administration in rabbits. Plasma and intravitreal concentration of DA-8159 was determined at each time point, and the electromicroscopic examination on retinal blood vessel was also performed. DA-8159 did not induce any significant difference in either a- or b-wave amplitudes. The implicit time of the a- and b-wave also did not show remarkable changes. In the highest dose group, however, mild and transient changes in rod and cone response were observed 1 hr after administration, which disappeared at 5 hrs post-dosing. Intravitreal concentration of DA-8159 was about half of the concentration of sildenafil after the same oral dose. There was no histopathological evidence of toxicity on retinal blood vessels. These data suggest DA-8159 has a lower risk potential of ocular side effects, but further evaluation of the effects of DA-8159 on visual functions in human must be performed.

[PA1-22] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Induction of penile erection in spinal cord-injured rabbits by administration of DA-8159, a new selective PDE 5 inhibitor

Ahn GookJun°, Kang KyungKoo, Baek DaeHyun, Sohn YongSung, Choi SeulMin, Ahn ByoungOk, Kwon JongWon, Kim WonBae

Dong-A Pharmaceutical Research Institute

DA-8159 is a new, highly selective, potent cyclic-GMP phosphodiesterase 5 inhibitor developed by Dong-A Pharmaceutical Company(Kyunggi, Korea) as an oral drug for the treatment of erectile dysfunction. NO- cGMP signal transduction pathway plays a key role for relaxation of corpus cavernosal smooth muscle. In this study, the efficacy of DA-8159 was evaluated by measuring the length of uncovered penile mucosa in spinal cord injury(SCI) rabbits. Spinal cord injury is regarded as one of the main risk factors for erectile dysfunction in human. In this study, SCI was induced by spinal cord transection at the local level(L2-L4) preventing the effective release of penile neurotransmitter, nitric oxide, from nonadrenergic-noncholinergic nerves. It was proven that penile erection was

induced in SCI-injured rabbits models after oral and IV administration of DA-8159(0.3mg/kg-10mg/kg). Furthermore, the efficacy was potentiated by administration of sodium nitroprusside. These results demonstrate that DA-8159 has a reliable and reproducible effect on penile erection in spinal cord injured rabbits.

[PA1-23] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Pharmacology of novel vanilloid receptor antagonists

Choi JinKyu°1, Yi JungBum1, Koh HyunJu1, Jeong YeonSu1, Lim KyungMin1, Moh JooHyun1, Suh YoungGer2, Oh UhTaek2, Kim HeeDoo3, Park HyeungGeun2, Park YoungHo1

1. Drug Discovery, AmorePacific Corporation R&D Center;2. College of Pharmacy, Seoul National University;3. College of Pharmacy, Sookmyung Women's University

Capsaicin and analogues are valuable analgesic agents when administered to mammals, including humans. However, their pungency, hypothermia and the effects on the cardiovascular and respiratory systems through their general activation of primary afferents severely limit their use. So competitive antagonists have been pursued as a novel pharmacological agent for analgesics, rather than agonists. We have identified a new class of potent and selective vanilloid receptor (VR) antagonists. These antagonists exhibit highly potent antagonistic activities in both $^{45}Ca^{2+}$-uptake and single channel patch clamp assays as well as analgesia in capsaicin test and PBQ writhing test. Furthermore, these compounds are devoid of the important shortcomings of capsaicin, such as hypothermia and pungency. These results suggest that VR blockade could be a novel therapeutic approach to analgesia.

[PA1-24] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

IN VIVO METABOLISM OF 2-METHYLAMINOETHYL-4,4'-DIMETHOXY-5,6,5',6'-DIMETHYLENEDIOXYBIPHENYL-2'-CARBOXY-2-CARBOXYLATE (DDB-S) BY LC/ESI TANDEM MASS SPECTROMETRY

Son Junghyun°, Lee Jaeick, Yang Ryung*, Kim DongHyun

Bioanalysis and Biotransformation Research Center, Korea Institute of Science and Technology, *Department of Biotechnology, Yonsei University

2-Methylaminoethyl-4,4'-dimethoxy-5,5',6,6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S) is a synthetic compound derived from DDB, which is protects liver against carbon tetrachloride-, D-galactosamine-, thioacetamine-, and prednisolone- induced hepatic injury in experimental animals. We assessed the use of liquid chromatography/electrospray iontrap tandem mass spectrometry (LC/MS/MS) method to identify and quantify in vivo metabolites and to measure excretion. DDB-S was administered intravenous to rats, and samples of urine, and feces were collected and analyzed by LC/MS. This method identified twelve metabolites in urine and feces. The major metabolic pathways of DDB-S in rats were identified as demethylenation of the methylenedioxyphenyl group and demethylation of the carboxymethyl moiety. The others were identified as demethylenation and demethylation, and glucuronidation.

[PA1-25] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Selectivity of the optical isomers of KR30031 on MDR reversal activity and cardiotoxicity