endothelial (eNOS) and neuronal (nNOS) isoforms which are constitutive and produce small quantities of NO, and an inducible isoform (iNOS) which is markedly induced in response to lipopolysaccharide (LPS) or inflammatory cytokines. Newly synthesized quinone derivatives were tested for their inhibitory effects on endothelial NOS (eNOS) by investigating the effect on endothelium-dependent relaxation of isolated rat aorta, and also tested for their inhibitory effects on neuronal NOS (nNOS) by measuring NOx (nitrate/nitrite) produced by NOS in rat forebrain homogenates. Among the tested compounds including twelve 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones (HPBIQ1-12), six 7-arylamino-5,8- quinazolinediones (SKH3, SKH5, SKH13, SKH15, SKH21, and SKH28), and two 6-arylamino-5,8-quinazolinediones (DQZ18 and DQZ21), SKH3, SKH5 and DQZ4 produced strong inhibitory effects on the acetylcholine-induced vasorelaxation of phenylephrine-precontracted aorta with the intact endothelium indicating their possession of inhibitory effect on eNOS, and also decreased nNOS activity by about 50% in rat brain at a tested concentration. Compounds SKH13, SKH15 and SKH21 produced moderate inhibitory effects on both eNOS and nNOS. None of HPBIQs showed inhibitory effects on eNOS, on the other hand, most of HPBIQs (except HPBIQ1 & 3) exhibited relatively strong inhibitory effects on nNOS. SKH28 and DQZ18 showed relatively weak inhibition of eNOS in rat aorta, but inhibited nNOS activity by about 50% in rat brain. This study found new quinone compounds which might be developed as NOS inhibitors with different selectivity.

[PA1-19] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Attenuation of monocrotaline-induced pulmonary hypertension with DA-8159, a potent PDE 5 inhibitor

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This study was carried out to demonstrate the effects of oral administration of DA-8159, a selective phosphodiesterase 5 inhibitor, on development of pulmonary hypertension induced by monocrotaline (MCT). MCT-treated rats(60mg/kg) were divided into three groups and orally administered vehicle, 1mg/kg or 5mg/kg of DA-8159 twice a day for 3 weeks. Increased right ventricular weights, medial wall thickening in pulmonary arteries, myocardial fibrosis, decrease of plasma cyclic guanosine monophosphate (cGMP) level and body weight gains were shown in MCT group. However, DA-8159 markedly and dose-dependently reduced the development of right ventricular hypertrophy and medial wall thickening. Furthermore, DA-8159 amplified the increase in plasma cGMP level and significantly increased the level of lung cGMP compared with MCT group. Although body weight gain was still lower from the saline-treated control group, DA-8159 demonstrated a significant increase in body weight gains both in 1mg/kg and 5mg/kg groups when compared with MCT group. In myocardial morphology, MCT-induced myocardial fibrosis was markedly prevented by DA-8159. These results suggest that DA-8159 may be useful oral treatment option for pulmonary hypertension.

[PA1-20] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

TOLERANCE AND PHARMACOKINETICS OF SINGLE-DOSE DA-8159, A SELECTIVE PDE5 INHIBITOR, IN HEALTHY MALES

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Tolerance and pharmacokinetics after single-dose administration of DA-8159, a new selective PDE5 inhibitor under phase I study, were examined in 42 healthy male volunteers in a six-period, double-

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

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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

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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