[PA1-17] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

The Oral Efficacy of DA-8159, a New Phosphodiesterase 5 Inhibitor, for Inducing Penile Erection in Concious Rabbits

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DA-8159 is a pyrazolopyrimidinone derivative showing potent and selective phosphodiesterase 5 inhibition. DA-8159 induced a dose-dependent increase in intracavernous pressure (ICP) in the anesthetized dog. The aim of this study was to investigate the oral efficacy of DA-8159 in a conscious rabbit model. DA-8159 and sildenafil citrate (0.3 to 10 mg/kg) was given orally or intravenously to awake male rabbits in the absence or presence of intravenous sodium nitroprusside, a nitric oxide donor. Erection was evaluated in a time-course manner by measuring the length of the uncovered penile mucosa. In results, both DA-8159 and sildenafil citrate induced a dose-dependent erection in conscious rabbits. The effective dose level and the duration of DA-8159 induced erection were comparable to those of sildenafil citrate. However, the onset time of erectile activity was slightly but significantly faster in DA-8159 treated animals than in the sildenafil citrate-treated rabbits. The oral efficacy of both drugs was potentiated and the effective doses were significantly decreased by intravenous sodium nitroprusside. Potentiation of the effect by a nitric oxide donor implies that DA-8159 would have enhanced activity during sexual arousal. These results clearly demonstrate that DA-8159 may be useful for treatment of erectile dysfunction.

[PA1-18] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Renal Action of Raclopride, a Dopamine D2 Receptor Antagonist, in Dog

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This study was attempted to investigate the effect of raclopride, a dopamine D2 receptor antagonist, on renal function in dog. Raclopride(70~220 ㎍/㎏), when given intravenously, produced antidiuresis along with the decrease in free water clearance(CH2O), urinary excretion of sodium and potassium(ENa, EK), partially decreased osmolar clearance(Cosm) and increased reabsorption rates of sodium and potassium in renal tubules(RNa, RK). Raclopride administered into a renal artery did not influence on renal function in small doses(10 and 30 ㎍/㎏), whereas exhibited the decrease of urine volume(Vol) and CH2O both in experimental and control kidney in much dose (100 ㎍/㎏), at this time, the decreased rates of both Vol. and CH2O were more prominent in control kidney rather than that elicited in experimental kidney, and then only ENa was decreased in control kidney, but increased in experimental kidney. Raclopride administered via carotid artery(30~200 ㎍/㎏) did not influence at all on renal function. Antidiuretic action induced by raclopride given intravenously was not affected by renal denervation. Raclopride given into carotid artery was little effect on renal function without relation to renal denervation. Above results suggest that raclopride produces antidiuresis by potentiation of antidiuretic hormone(ADH) action in blood without increase of ADH secretion in posterior pituitary gland, it is not related to renal nerve function in dogs.

[PA1-19] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Studies on Safety Pharmacology of DA-8159, a New Erectile Dysfunction Treatment

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Safety pharmacological properties of DA-8159, a new pyrazolopyrimidinone derivative were examined in laboratory animals to investigate its safety profile. The oral administration of DA-8159 (1, 5 or 30 mg/kg) in mice and rats had no effect on general behaviors and central nervous system of the animals in test systems, such as hexobarbital-induced sleeping time, motor coordination, normal body temperature, writhing syndromes induced by 0.75% acetic acid solution, chemo-shock produced by pentetrazole solution and rotar rod test. Anesthetized cats treated intravenously with DA-8159 (0.1, 0.3, 1, 3 or 10 mg/kg) showed transient and mild decrease in blood pressure. However, heart rate, respiration rate and tidal volume were not changed by intravenous DA-8159. In the isolated organs including ileum, heart (sinus rate of atria and contractility of papillary muscle), trachea of guinea pigs and phrenic nerve of rats, DA-8159 ($10^{-8} \sim 10^{-5}$ g/mL) did not elicit any effect or inhibitory action on the chemically or electrically stimulated contraction. DA-8159 did not influence gastric secretion, pH and total acid output in rats and intestinal propulsion in mice. The administration of DA-8159 in rats had no effect on the platelet aggregation induced by ADP in rabbit plasma, urinary volume and electrolyte ion (Na^+, K^+, Cl^-) excretion in rats. Prothrombin time (PT) of the rats showed a mild but significant increase after administration of DA-8159. Activated partial thromboplastin time (APTT), however, was not affected by DA-8159. These results indicate that DA-8159 does not exert any of serious pharmacological effects.

[PA1-20] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Effect of Resveratrol on Dimethylnitrosamine-Induced Liver Fibrosis in Rats

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Resveratrol (trans-3,4',5-trihydroxystilbene), a polyphenolic compound found in grapes was reported to inhibit activation of hepatic stellate cells *in vitro*. In this study, we have evaluated the preventive effect of resveratrol on liver fibrosis induced by dimethylnitrosamine (DMN) in rats. Oral administration of resveratrol significantly prevented the DMN-induced loss in body weight and liver weight. Resveratrol inhibited dramatically the elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in DMN-induced liver injuries, and improved the serum albumin concentrations. Resveratrol also prevented the increase collagen deposition and reduced MDA contents in the liver. These results suggest that resveratrol may be potentially useful in the prevention of the development of hepatic fibrosis.

[PA1-21] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Effects of SK-1080 on neointimal formation after rat carotid artery balloon angioplasy

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We investigated the effects of SK-1080, a novel angiotensin AT1 receptor antagonist, on neointimal proliferation in the rat carotid artery after balloon injury, together with its effects on the impaired endothelium-dependent vascular relaxation. SK-1080 (0.3 and 1.0 mg/kg/day) was orally administered in balloon injured rats for 21 days (from 6 days before to 14 days after balloon injury). SK-1080 (1 mg/kg) exerted significant effects on three important parameters associated with the intimal thickening induced by balloon injury (50.0% reduction in neointimal area, 42.7% reduction in stenosis ratio and 69.1% increase in lumen/total area ratio). Acetylcholine-induced relaxation was significantly reduced in the balloon injured carotid arteries (64.0 □, 9.1%), and this impairment of acetylcholine-induced relaxation was significantly restored by SK-1080 (Maximal relaxation: 87.1 □, 6.5 and 88.6 □, 1.9% at 0.3 and 1.0 mg/kg, respectively, $p<0.05$). However, the endothelial-independent, sodium nitroprusside-