The present study was performed to compare the cardiovascular adverse effects of verapamil, KR30031 and their each optical isomers, and also to measure their ability to overcome multidrug resistance (MDR). R-isomer of KR30031 (R-KR30031) was equipotent with S-isomer of KR30031 (S-KR30031) and 25 fold less potent than R-isomer of verapamil (R-verapamil) in relaxing the aorta isolated from rat (EC50: 11.8, 10.2 and 0.46 μM, respectively). The effect of R-KR30031 in decreasing left ventricular pressure of heart isolated from rat was 2 and 26 fold smaller than those of S-KR30031 and R-verapamil, respectively (EC50: 23.9, 9.4 and 0.089 mM, respectively). The hypotensive effect of R-KR30031 in rat was about 2 and 23 fold smaller than those of S-KR30031 and R-verapamil, respectively (ED20: 1.15, 0.60 and 0.05 mg/kg, respectively). On the other hand, R-KR30031 elicited potency similar to those of S-KR30031 and R-verapamil in enhancing the paclitaxel-induced cytotoxicity to HCT15/CL02 and MES-SA/DX5 cells that reveal high level of PGP expression (IC50: 3.11, 3.04 and 2.56 μM, respectively). In addition, the intrinsic cytotoxicity of R-KR30031 in HCT15/CL02 and MES-SA/DX5 cells was observed only at the very high concentration of 100 μM. All these results suggest that R- and racemic KR30031 are active modulators of MDR with potentially minimal cardiovascular adverse activity.

[PA1-26] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

DA-7911, rhenium-188 (Re188) tin colloid, as a strong candidate agent for radiation synovectomy

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Radiation synovectomy is an useful alternative treatment to rheumatoid arthritis and Re188 is suggested as an ideal radiopharmaceutical agents because beta ray (2.1 MeV) emitted from Re188 is appropriate for synovial cell ablation and gamma ray (155 KeV) is ideal for dosimetry. Its' ideal particle size (2-5 mm) was achieved by conjugation with tin-colloid. In this study, we investigated the toxicity, stability and biodistribution to evaluate the suitability of DA-7911 as a synovectomy agent. In acute toxicity of DA-7911 in ICR mice (i.v.), the value of LD50 was 60.9 mCi/kg. In vitro stability tests, DA-7911 remained as a colloid form without critical size variation over a 2-day period. In the normal rats, the leakage test from the intraarticular injection site with gamma counting showed that the mean retention percentage of DA-7911 was 98.7% at 1 day. In biodistribution study, the liver produced the highest radioactivity (0.0427% ID/organ) except for the injected knees. After animal experiments, we performed radiation synovectomy in 22 knees from 21 rheumatoid arthritis patients who were refractory to local corticosteroid injection. We evaluated the efficacy and safety of DA-7911 from 3 months up to 23 months after the injection of 10-30 mCi of Re188-tin colloid. In visual analogue scale, pain (86.3 %), joint tenderness (63.6 %), swelling (86.3 %) and range of motion (72.7 %) were improved. In blood, activity of Re188 was 0.009 %/injection dose. There were no abnormalities in complete blood count, liver function test and urine analysis in any patients, although transient reactive synovitis was observed in 18 cases (81.8 %).

In conclusion, DA-7911 is a strong candidate agent for radiation synovectomy with its superior efficacy and safety.

[PA1-27] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]
Comparison of CYP 3A4 metabolism between DA-8159 and Sildenafil in vitro and in vivo

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DA-8159 is a new PDE5 inhibitor, synthesized by Dong-A Pharm., as an oral agent to treat male erectile dysfunction. DA-8159 and sildenafil are mainly metabolized by cytochrome P450 enzyme CYP 3A4. In this study, we compared the metabolism of DA-8159 with sildenafil in vitro and in vivo. First, we quantified the remaining ratio of original compound, DA-8159 and sildenafil, after we incubated drugs for 30 minutes with human liver microsome cytochrome P450 3A4. The remaining ratio of DA-8159 is higher than sildenafil (Sildenafil: 19.76%, DA-8159: 50.67%). In vivo experiment, we examined changes in the drugs metabolism when we inhibited CYP 3A4 by the ketoconazole administration in rats. When CYP 3A4 is inhibited, AUC0–8 of sildenafil was increased by 352.75%. On the hand, AUC0–8 of DA-8159 was increased by only 44.10%. It means that sildenafil is more metabolized than DA-8159 by CYP 3A4. Therefore, it is considered that the drug interaction of DA-8159 is less than that of sildenafil.

[PA1–28] [ 10/18/2002 (Fri) 09:30 - 12:30 / Hall C ]

Synthesis and Evaluation of Biological activities of New Imine Derivatives of Apicidin

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Apicidin, a natural product HDAC inhibitor, is recently isolated from Fusarium sp, at Merk Research Laboratories, induces therapeutic applications as a broad spectrum antiprotozoal agent to multi-drug resistant malaria and a potential antitumor agent. The biological activity of apicidin appears to be apicocomplexan HDAC at low nanomolar concentrations. In since, we have worked about the synthesis and the evaluation of biological activities of various derivatives of apicidin, we have discovered that apicidin and some derivatives have mild antitumor activity, which change the morphology of tumor cells to the one of normal cells. As part of our program toward the development of new antitumor agents, we synthesized its derivatives systemically, and then studied their structure–activity relationships. At present, we modified the ketone moiety of apicidin to obtain various imine derivatives in consideration of interaction with HDAC

[PA1–29] [ 10/18/2002 (Fri) 09:30 - 12:30 / Hall C ]

Revers phase HPLC Separation of D-Amygdalin and Neoamygdalin and Optimum Conditions for Inhibition of Racemization of Amygdalin

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