The repeated dosing toxicity tests of a novel solubilizer for paclitaxel in male beagle dogs

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Paclitaxel isolated from the pacific yew tree, Taxus brevifolia, is microtuble-stabilizing agent that has a promising anticancer activity against a wide variety of tumors such as ovarian, breast and lung cancers. Because of its poor water solubility, paclitaxel is currently formulated in a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol USP (1:1 v/v). The major obstacles for successful chemotherapy with paclitaxel are the toxic side effects due to the use of conventional solubilizer, Cremophor EL. We have tried to develop a new solubilizer for paclitaxel to improve efficacy and to reduce toxicity of solubilizer. We previously reported that Aceporol 330 showed the most favorable results from the paclitaxel-stabilizing test and the hemolysis test, and less toxicity than cremorphor EL in female beagle dog In the present study, we have performed the 2-week repeated dosing toxicity test of Aceporol 330 in the male beagle dogs. After 2-week intravenous administration of Aceporol 330 at a dose of 1ml/kg/day, the effects of Aceporol 330 on the body weights, the comsumption of water, food uptake, urinalysis, the organ weights, hematological test, serum biochemical tests and histopathological tests were evaluated, and no significant abnormality was found, except the increase of total cholesterol level in the Aceporol 330 or Cremophor EL treated group compared that of untreated control group. During administration of Aceporol 330, vomiting and diarrhea were observed but much less extent than Cremophor EL. Taken together, these data indicates that Aceporol 330 seems to show more tolerance than Cremophore EL when they were given to beagle dog as well as mouse.

[PA4-9] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Inhibition of CYP1a1 activity by COX-inhibitors in C57BL/6 mouse and Hepa I cells.

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In order to understand the mechanism of action of TCDD, we have examine the effect of COX-inhibitors on CYP1a1 activity. We observed the effect of COX-inhibitor on EROD activity in C57BL/6 mouse in vovo. And we also evaluated the effect of COX-inhibitors on both mouse cyp1a1 promoter activity in Hepa cell and human CYP1A1 promotor activity in MCF-7 cell. There have been known two isoforms of COX enzyme. COX-1 is known as the housekeeping enzyme and COX-2 is inducible by inflammatory stimuli. NSAID such as aspirin and celecoxib, seems to inhibit reversibly COX. Aspirin is an non-selective COX inhibitor and celecoxib is an COX-2 specific inhibitor. When COX-inhibitor such as Aspirin and Celecoxib were pretreated with TCDD in vivo, the EROD activity that was stimulated by TCDD was inhibited. And Pretreatment of aspirin and celecoxib in vitro, inhibited the TCDD stimulated Luciferase activity. For the action of COX inhibitors such as aspirin and celecoxib on the CYP1A1, it seems to be important to do pretreatment of these chemicals before TCDD. In this study, thus, we have suggested that COX-inhibitors such as aspirin and celecoxib, decrease the TCDD induced cyp1a1 and CYP1A1.

[PA4-10] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

PCB-induced Cytotoxicity in Catecholaminergic CATH.a Cells related to Inhibition of NO Production

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The neuronal nitric oxide synthase (nNOS) specific inhibitor, 7-nitroindazole (7-NI), and the nitric oxide (NO) donor (S-nitroso-N-acetylpenicillamine: SNAP) were used to study the role of NO in polychlorinated biphenyl (PCB: Aroclor 1254)-induced cytotoxicity in the immortalized dopaminergic cell line (CATH.a cells), derived from the central nervous system of mice.
Treatment of the CATH.a cells with various concentrations of Aroclor 1254 (0.5-10 μg/ml), a commercial PCB mixture, showed significant cytotoxicity as evaluated by LDH release and assessment of cell viability, depending on the concentrations used. We also observed that Aroclor 1254 treatment reduced the level of nNOS expression and activities. Furthermore, the cytotoxicity of Aroclor 1254 was augmented by 10μM of 7-NI, which alone did not produce cytotoxicity, while it was protected by treatment with SNAP. Therefore, these results suggest that PCBs have the potential for dopaminergic neurotoxicity, which may be related with the PCBs-mediated alteration of NO production originating from nNOS. Depending on the concentrations of Aroclor 1254 used, intracellular dopamine concentrations were significantly decreased. Also, the metabolic pathway of dopamine to dihydroxyphenylacetic acid (DOPAC) was not altered by Aroclor 1254 treatment.
Thus, we suggest that Aroclor 1254 alters NO-mediated control of intracellular dopamine, which is a possible mechanism of the Aroclor 1254-induced cytotoxicity, at least in part.

[PA4-11] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

CCl4-induced Lipid Peroxidation and Acute Liver Fibrosis in the Rat

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Oxidative stress and its consequent lipid peroxidation exert harmful effects, which have been currently involved in the generation of carbon tetrachloride-induced cirrhosis. In this study, we investigated whether lipid peroxidation can be associated with liver fibrosis(cirrhosis) in CCl4-induced rats, and CCl4-induced model used in this study is suitable as screening of lipid peroxidation and liver fibrosis(cirrhosis). The female Sprague-Dawley rats were divided in 2 groups(Normal, CCl4) and were observed in 3 weeks. Except for normal, the rats rendered fibrotic(cirrhotic) by CCl4 administration(0.6㎖/rat/week) for 3 weeks. In the result, the hepatomegaly appeared in CCl4 group, and significantly higher liver weight and liver/body weight ratio were observed in CCl4 group compared with in normal group($p<0.001$). The value of clinical parameters in sera were significantly increased in CCl4-induced rats($p<0.001$). Especially, the value of MDA and the content of hyp in CCl4 group significantly increased 1.3~1.7 times than in normal group($p<0.05$, $p<0.001$). Our data indicate that lipid peroxidation and liver fibrosis(cirrhosis) can be observed in liver fibrosis-induced rats by CCl4 administration for 3 weeks. Furthermore, we suggest that lipid peroxidation may be a link between tissue injury and fibrosis in CCl4-induced rats, and CCl4-induced rat model used in this study can eliminate problem of already well known CCl4-induced experimental model.

[PA4-12] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Effect of all trans retinoic acid and 9-cis-retinoic acid on human breast cancer MCF-7 cell proliferation.

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We have examine the effect of all trans retinoic acid and 9-cis-retinoic acid on human breast cancer cell proliferation using SRB assay and cell cycle analysis. 1)In MCF-7 cells, in the presence of phenol red, either all trans retinoic acid or 9-cis-retinoic acid treatment showed the inhibition of the cell proliferation over control cells and also inhibit the estrogen stimulated cell proliferation when it was given together with estrogen. When either all trans retinoic acid or 9-cis-retinoic acid treatment in the presence of tamoxifen, it did not affect the effect of tamoxifen. 2) In MCF-7 cells, in the absence of phenol red, all trans retinoic acid alone treatment showed slight increase in cell proliferation over control cells and inhibit the estrogen stimulated cell proliferation when it was given together with estrogen. 9-Cis-retinoic acid alone treatment did not affect the cell proliferation but inhibit the estrogen stimulated cell proliferation when it was given together with estrogen. When either all trans retinoic acid or 9-cis-retinoic acid treatment in the presence of