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.

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

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