

Chromosome aberration study of tetrahydroisoquinoline compounds, THI52 and THI53 as a drug candidate of the cardiovascular system

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To clarify the toxicity of tetrahydroisoquinoline compounds THI52 and THI53, as a drug candidate of the cardiovascular system, we performed the chromosome aberration assay with Chinese hamster lung (CHL) cell lines. First of all, we decided the 50% cell growth inhibition concentration (IC_{50}) of THI52 and THI53 to set the dose-range in CHL cells. The IC_{50} of THI52 and THI53 were 24.3 and 22.08 $\mu\text{g/ml}$ in the presence of S-9 metabolic activation system, and 8.27 and 8.72 $\mu\text{g/ml}$ in the absence of S-9 metabolic activation system, respectively. In CHL cells exposed to THI52, no significant increase of chromosome aberration was observed in the absence of (2.07-8.27 $\mu\text{g/ml}$) S-9 metabolic activation system. However, in the presence of (6.1-24.3 $\mu\text{g/ml}$) S-9 metabolic activation system, the chromosome aberration was significantly increased. In CHL cells exposed to THI53, no significant increase of chromosome aberration was observed in the absence of (2.18 - 8.72 $\mu\text{g/ml}$) S-9 metabolic activation system. In presence of (22.08 $\mu\text{g/ml}$) S-9 metabolic activation system, however, the chromosome aberration was significantly increased. From these results, THI52 and THI53 revealed no chromosome aberration in the absence of S-9 metabolic activation system in CHL cells. But, in the presence of S-9 metabolic activation system the significant increase of chromosome aberration was observed.

[PA4-7] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Measurement of CYP1A1, GST mRNA in monkey brain, intestine, liver.

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The induction of specific P-450 enzymes is difficult to study in man, but non-human primates may provide useful models for this purpose. Previous investigation have shown that phenobarbital, 3-methylcholanthrene(3MC) and TCDD induce several P-450 enzymes in the liver and several extrahepatic organs of monkey. The aim of this study was to determine whether treatment of monkeys with 3MC and dibutylphthalate(DBP) causes an induction of CYP 1A1 as a phase I drug metabolizing enzyme, and GST mRNA as a phase II drug metabolizing enzyme in brain, intestine and liver of monkey.

Treatment of monkey with 3MC resulted in a induction of CYP 1A1 mRNA in brain(3-fold), intestine (2.5-fold), and liver(6-fold). But treatment with DBP not significantly induced CYP 1A1 mRNA. The basal level and induction of neonatal monkey CYP 1A1 mRNA is low, compared to that of adult monkey. Treatment with both 3MC and DBP induced GST α , μ , π . The induction of GST α , μ and π is 1.5-2.5fold.

[PA4-8] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Differential histopathological effect of glycolic acid, TPA and UVB irradiation in guinea pig skin

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Alpha-hydroxy acids (AHAs) are used in cosmetic products as pH adjuster, mild exfoliant and humectant-skin conditioner. Cosmetics containing high concentration and low pH of AHAs can cause side effects such as epidermal crusting and necrosis, whereas low dose of AHA induces thickness of stratum corneum. In this study, we examined histopathological effect of glycolic acid on guinea pig skin. We also compared with the effects of phorbol 12-myristate 13-acetate (TPA) and UVB irradiation. Different doses of glycolic acid (10 to 70%, pH 3.0), TPA (0.1 mM) and UVB irradiation (0.4 and 3 J/cm²) were treated on back skin of guinea pig for 14 days. Histological changes were examined with hematoxylin-eosin staining method. The epidermis got thicker in glycolic acid-treated skin compared with control. More than 50% of glycolic acid caused disruption of normal skin structure. The thickness of epidermis in UVB-irradiated skin also increased, but that in TPA treated-skin did not. Glycolic acid induced hyperplasia in epidermis (keratinocytes) at 10% to 70%, and induced necrosis of the cells in epidermis at more than 30%. Glycolic acid induced hyperplasia and necrosis of cells in dermis (fibroblast) at 50% and 70%. TPA induced necrosis of the cells in epidermis and dermis and infiltration of inflammatory cells (lymphocytes and eosinophilic cells). The number of apoptotic cells was increased by glycolic acid and UVB treatment. These results show that the examined chemicals and UVB irradiation caused differential skin responses.

[PA4-9] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Study of DK-35C, a carbapenem antibiotics, in forward gene mutation assay in L5178Y mouse lymphoma cells and in vivo cytogenetic assay

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To investigate the toxicity of a carbapenem antibiotics DK-35C, we performed the forward gene mutation assay in L5178Y mouse lymphoma cells and *in vivo* supravital cytogenetic assay in mice. In forward gene mutation assay with L5178Y mouse lymphoma cell, DK-35C revealed statistically significant increase in mutation frequency (MF) at the highest dose (1250 µg/ml) in the absence of metabolic activation system. However, no significant increase of MF was observed in the presence of S-9 metabolic activation system at concentrations (625~5000 µg/ml) used. In supravital staining micronucleus assay with mouse peripheral reticulocytes, no significant increase of micronucleated reticulocytes(MNRETs) was observed after intraperitoneal administration of DK-35C (463.3, 231.7, and 115.9 mg/kg) to mice. From the results that chromosomal aberration previously reported and MNRETs in mouse reticulocytes were not induced by DK-35C, this data indicate that DK-35C itself may induce some point mutation at the high concentration.

[PA4-10] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Metabolic Phenotyping and Genotype of Dextromethorphan

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The abuse of dextromethorphan has been prevalent for longer than 10 years in Korea and its fatal cases were reported even though it has proved to be very safe. In this study, to investigate the safety and tolerance assesment of dextromethorphan, the metabolic phenotyping and genotype of dextromethorphan were studied. After a single 30mg dextromethorphan oral administration to 60 volunteers, dextromethorphan and its metabolites, dextrorphan, hydroxymorphinan and methoxymorphinan concentrations were measured