In conclusion, this study shows that NOV is strongly expressed during liver fibrogenesis, and hepatic stellate cells seems to be the major cellular sources of NOV in the liver.

Poster Presentations - Field E2. Pharmacokinetics

[PE2-1] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Quantitification of costunolide in rat plasma by HPLC

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Simple and precise high-performance liquid chromatographic (HPLC) assay was developed and validated for the determination of a sesquiterpenelactone material, costunolide in rat plasma. The method involved liquid liquid extraction of costunolide and internal standard partenolide. Samples were analyzed by reversed-phase HPLC using Capcell-Pak C18 column with ultraviolet detection at 230nm. The quantitation limit of costunolide was 0.05ug/ml and the calibration curve was linear over the range of 1-50ug/ml (r2>0.999) with human plasma. The analytes of quality control samples indicated that the normal values could be predicted with an accuracy >97%. The intra- and inter-day coefficients of variation for the analytes were <10%. We are undergoing the invivo pharmacokinetic study using these validation method.

[PE2-2] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Determination of YH3945 in beagle dog plasma by high performance liquid chromatography: validation and longterm stability

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YH3945, a non-peptide farnesyltransferase inhibitor, is being developed by Yuhan Research Institute for the treatment of cancer. The development and validation study of a sensitive, rapid, reproducible, accurate and precise high performance liquid chromatographic (HPLC) method for YH3945 in beagle dog plasma has been carried out and the longterm stability of YH3945 in beagle dog plasma has been investigated. Plasma was extracted with acetonitrile containing the internal standard. An aliquot of the extract was injected onto a reverse C18 column. Retention times of YH3945 and the internal standard were 6.9 and 10.6 min, respectively. The chromatograms showed no endogenous peaks from blank plasma at the retention time of YH3945. Standard curves of YH3945 was linear over the range of 100 ng/ml to 10000 ng/ml (r=0.9995). The lower limit of quantification of YH3945 in plasma was 100 ng/ml. This assay also showed good inter- and intra-precision and accuracy throughout the concentration range. Precision expressed as C.V. was in the 1.2 to 4.6% range. Accuracy expressed as mean R.E. was between -0.9 and 5.5%. The extracted samples of YH3945 were stable at room temperature for 72 hours. The spiked plasma samples of YH3945 remain stable under frozen condition for 6 months, under ambient condition for 4 hours, and under a period of three freeze/thaw cycles. This sensitive, accurate and precise method can be applied to determine concentration of YH3945 in plasma for pharmacokinetic studies in beagle dogs.
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[PE2-3] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Pharmacokinetics and Bioequivalence of Tiropramide in Human Volunteers

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Two formulations of tiropramide {(±) α-(benzoylamino)-4-[2-(diethylamino)-ethoxy]-N,N-dipropyl-benzenepropanamide hydrochloride}, an antispasmodic agent, were orally administered to 16 healthy volunteers by the Latin crossover design with the purpose of evaluating bioeqivalence and pharmacokinetics of tiropramide. Tiropramide in human plasma was determined by a gas chromatography/nitrogen phosphorus detector. Detection limit of tiropramide was 5 ng/ml. C_{max} in test and reference formulations was 93.9 ±54.3 and 96.4 ±51.6 ng/ml, respectively. $AUC_{0\rightarrow last}$ and $AUC_{0\rightarrow inf}$ were, respectively, 330.7 ±193.9 and 349.5 ±205.3 ng.hr/ml for test formulation, 348.9 ±207.7 and 380.8 ±239.0 ng.hr/ml for reference formulation. Terminal half-life was 2.3-2.6 hr. Bioavailability differences for C_{max} and $AUC_{0\rightarrow last}$ were 2.48% and 5.22%, respectively. Minimum detection differences were less than 20 % in both C_{max} and AUC. Based on this results, two formulations of tiropramide were considered to be bioequivalent.

[PE2-4] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

pharmacokinetics of paclitaxel in rabbits with carbon tetrachloride-induced hepatic failure

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Pharmacokinetic of paclitaxel was investigated in rabbits with carbon tetrachloride-induced hepatic failure. The AUC of paclitaxel was significantly increased in severe hepatic failure rabbits(1364ng/ml.hr)compared to that of normal rabbits(567ng/ml.hr). The volume of distribution of paclitaxel in severe hepatic failure rabbits was significantly decreased compared to that of normal rabbits.Total body clearance of paclitaxel in severe hepatic failure rabbits(0.733) was significantly decreased compared to that of normal rabbits (1.762).This results could be due to inhition of paclitaxel metabolism in liver disorder rabbits since paclitaxe is essentially metabolized in liver. this findings suggest that the dosage regimen of paclitaxel should be adusted when the drug would be administered in patients with liver disorder in a clinical situation.

[PE2-5] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Tissue distribution study in CDF1 mice bearig solid lung tumor after administration of thermosensitive drug AspPt

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AspPt is a thermosensitive anti-tumor drug conjugate for local delivery of the drug to solid tumors. The platinum distribution of AspPt was compared with that of cisplatin in nude mice bearing solid lung tumor after single dose treatment. Various main organs such as liver, lung, heart, brain, tumor, kidney and whole blood were collected at 1, 5, 12, 24, 48 hours after intra-tumor administration. After digestion with HNO3 and then H202, Pt was measured with inductively coupled plasma-mass spectrometry(ICP-MS). Platinum concentration at tumor after AspPt was significantly higher, whereas this concentration at other organs was much less than those of cisplatin. Based on these results, this novel platinum(II) thermosensitive compound (AspPt) represents a valuable lead in the development of a new anticancer chemotherapeutic agent capable of improving antitumor activity and low nephrotoxicity.

[PE2-6] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]