[PE1-20] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Identification of JG-381 metabolite in rats

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JG-381, an etomoxir derivative, is a hypoglycemic agent that has been developed as a new drug candidates for the treatment of the diabetes. In our previous study, we found that Caco-2 permeability of JG-318 appears adequate for the oral formulation for the drug and that the compound is extremely unstable in the presence of plasma protein. Because of the instability of the drug, the parent drug concentration was not detectable in all blood samples that are collected 3 min after the intravenous administration, indicating that the compound is rapidly converted to its metabolite in the presence of plasma protein. Because serum albumin is known to catalyze de-esterification, we hypothesize that the product of the conversion in the presence of plasma protein is de-esterified form(s) of JG-381. Two potential degradation products of JG-381, diol-acid and epoxide-acid, were chemically synthesize and the chemical properties compared with that found in in vitro. Chromatographic and spectrometric comparisons indicated that the epoxide-acid form is consistent with the degradation form found in in vitro. Subsequently, JG-381 was administered to rats to determine whether the metabolism occurred in in vivo. The epoxide metabolite was readily detectable in all plasma samples collected from rats that received iv administration of JG-381. Considering that hypoglycemic activity is well documented in rats for JG-381 and that the parent drug is rapidly de-esterified in the animal, the epoxide metabolite of JG-381 may be responsible, at least in part, for the anti-diabetic activity of the etomoxir derivative.

[PE1-21] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics of the Paclitaxel of New Micelle Formulation

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Paclitaxel is a antitumor agent with poor water solubility and its pharmacokinetics are nonlinear. Cremophor EL, a surfactant used in the formulation of paclitaxel, may cause adverse effects. Alternative drug delivery systems are under development in recent years to reduce drug toxicity and improve efficacy. We studied pharmacokinetics of novel polymeric micellar paclitaxel with new solubilizers, Aceporol 330(BLK330) and GO460(BLK460), in rat. The formulations of Paclitaxel diluted with 5% glucose injection was administerd at 5mg/Kg by iv infusion in rat. Plasma were collected between 2 min and 4 h after administration. The of BLK330, BLK460 and Taxol were 1025.28㎍L-1min, 481.50㎍L-1min and 818.820㎍L-1min. When we added 7, 15 and 30mg of ascorbyl palmitate to BLK460, the were changed to 289.39㎍L-1min, 394.12㎍L-1min, 892.83㎍L-1min.
The surfactant of micellar paclitaxel can alter the blood distribution. We evaluated the linearity of BLK330. Mice received paclitaxel by iv injection at 2.5, 5 and 10mg/Kg by dilution of the formulations of paclitaxel with 5% glucose injection. Whole blood and plasma were collected up to 24 h after administration. Pharmacokinetics of paclitaxel were evaluated using whole blood and plasma. Paclitaxel was quantified by HPLC with UV detection at 227nm.

[PE1-22] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Thermosensitive liquid suppository containing diclofenac sodium : in vivo evaluation in rats

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Solutions of poloxamers and sodium chloride were previously reported to undergo a phase transition to bioadhesive gels at body temperature. For the development of a thermosensitive diclofenac sodium-containing liquid suppository, here we studied the dissolution and pharmacokinetics of diclofenac sodium delivered by the liquid suppository systems composed of poloxamer P 188, P 407 and sodium chloride. Poloxamer P 188 delayed the dissolution rates of diclofenac sodium from liquid suppositories. However, sodium chloride showed no significant effect on the dissolution rates of diclofenac sodium from liquid suppositories. Dissolution mechanism analysis showed the release of diclofenac sodium was proportional to the time. The initial plasma concentrations of diclofenac sodium in the liquid suppository [diclofenac sodium/P 407/P 188/sodium chloride (2.5/15/17/0.8%)] were significantly higher compared with those in solid suppository. Furthermore, it gave significantly faster Tmax of diclofenac sodium than did solid suppository, indicating that the diclofenac sodium from liquid suppository could be absorbed faster than that from solid one in rats. It did not cause any morphological damage to the rectal tissues. These results suggested that thermosensitive liquid suppository with sodium chloride could be a more physically stable, effective and convenient rectal delivery system of diclofenac sodium.

[PE1-23] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics of new solubilizer in the intravenous micelle formulation of paclitaxel

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New solubilizer (Aceporol 330, Aceporol 460) were developed to reduce side-effect of CrEL and increase the effect of drug as surfactant used in the intravenous micelle formulation of anticancer drug paclitaxel. We studied easy, rapid quantitative determination of Aceporol 330, Aceporol 460 in rat plasma samples, which was achieved by complexation of the compound with the Coomassie brilliant blue G-250 dye in protein-free extracts. The binding of the dye to Aceporol 330, Aceporol 460 caused a shift in the absorption maximum from 400nm to 700nm. The assay permited estimation of Aceporol 330, 460 concentrations in the range 0.3-10.0μL/mL. Pharmacokinetics of new solubilizer was studied by this method. Rats were treated with Aceporol 330, 460, each at dose levels of 18.8, 14.6 and 11.3mL/m2. Rat samples were collected up to 5h after start of infusion. AUC(0-300) of Aceporol 330, 460 were 6834.08μL.min/mL, 482.26μL.min/mL(at 18.8mL/m2), 4569.11μL.min/mL, 675.86μL.min/mL(at 14.6mL/m2) and 2924.50μL.min/mL, 335.95μL.min/mL(at 11.3mL/m2). Also, we investigated pharmacokinetics of anticancer drug paclitaxel and BLK 330, BLK 460 containing Aceporol 330, 460. When we compared pharmacokinetics of new solubilizers and BLK 330, BLK 460, results revealed that new solubilizers had not effect on tmax of paclitaxel but they affected at Cmax of paclitaxel.

[PE1-24] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Does hepatic ATP level significantly affect on the functional activity of the P-glycoprotein, ATP binding cassette transporter, in Protein Calorie Malnutrition?

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Protein Calorie Malnutrition(PCM), another form of oxidative stress, may alter the hepatic ATP activity and synthesis. Also, to know the expression and functional activity of P-glycoprotein(P-gp), one of the ATP binding cassette(ABC) transporters, is important, because several disease states can lead to malnutrition and may change the pharmacokinetics of P-gp substrates including anticancer agents, AIDS drugs.In this study, examined the effect of PCM in rats on the expression and functional activity of P-gp and on the biliary excretion of daunomycin, P-gp substrates and TEA.