[PE3-1] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics and liver targetability of methotrexate-lactosylated albumin conjugates

Han Junghee°, Kim Chong-Kook

Toxicology Research Center, Korea Research Institute of Chemical Technology, Yusong, Daejon 306-600, Korea

Purpose. To study whether we could enhance the liver targeting of anticancer agent via asialoglycoprotein receptors using conjugates of MTX-variously lactosylated bovine serum albumin.
Methods. methotrexate (MTX) was conjugated with albumin previously substituted with varying content of lactose (L0, L5 and L24). The uptake of MTX by rat hepatocyte in vitro and the MTX level in the plasma and various organs was determined by counting the radioactivity of MTX and by HPLC assay, separately to monitor the in vivo fate of MTX not only as total, regardless of forms of MTX, but also as free/intact MTX level.
Results. Conjugation of MTX with albumin alone provided the enhanced delivery of MTX to the liver, accompanied by decreased accumulation in the kidney, but by increased accumulation in other non-target organs such lung, heart and spleen. Lactosylation of albumin conjugates further enhanced the delivery of MTX to the liver in a lactose content-dependent manner, accompanied by decreased accumulation of MTX in the lung and heart as well as kidney. The total MTX level accumulated in the liver was 2.9-, 4.1- and 11.0- fold higher at 1 h and 5.4-, 7.0- and 16.5- fold higher at 4 h after injection of MTX-L0, L5, L24 albumin conjugates compared with MTX alone. MTX conjugates with lactosylated albumin provided low but prolonged level of free/intact MTX in the liver.
Conclusions. The pharmacokinetics and liver targetability of MTX could be favorably modulated by controlling the lactose content on the albumin conjugates. Lactosylated albumin conjugation might also provide a potential for the prolonged and targeted delivery of other drugs for the treatment of liver diseases.
Acknowledgement. This research was partly supported by the grant from National Research Laboratory Program (Lab No 87) in the series of MOST-NRDP in the Ministry of Science and Technology, Korea.

[PE3-2] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Dissolution Behaviors of Various Commercial Preparations in Different Dissolution Medium Compositions

Jin SungGiu°, Kim TaeWan, Cao QingRi, Choi ChoonYoung, Lee BeomJin

College of Pharmacy, Kangwon National University

The differences in dissolution behaviors of commercial preparations using different compositions of dissolution media were investigated. The immediate release itraconazole (ITR-IR) and acyclovir(ACV-IR) and sustained release nifedipine (NIF-SR) preparations were chosen. The composition of dissolution media used was simulated gastric fluid (SGF) or simulated intestinal fluid(SIF) with tween 80, sodium lauryl sulfate(SLS), pepsin, pancreatine, and 3.5% fat milk, respectively. The dissolution behaviors were evaluated using USP dissolution method II (paddle). In case of ITR-IR, addition of SLS and pepsin

resulted in increase of dissolution rate. The milk did not affect the dissolution. The effect of dissolution media was more predominant in SIF due to poor solubility of ITR. Dissolution rate of ACV-IR was rather decreased in the presence of surfactants in both SGF and SIF. On the other hand, sustained release rate of NIF-SR was highly affected by the dissolution media in both SGF and SIF. The release rate was highly increased when surfactants(SLS and Tween) were added. Dissolution rate was shown to be dependent on formulation and dissolution medium, especially class II drugs (ITR, NIF) due to their poor solubility. This work was supported by grant No 2000-1-21700-001-3 from the Korea Science & Engineering Foundation.

[PE3-3] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Preparation and evaluation of bupivacaine microspheres by a solvent evaporation method

Lee Sibeum, Woo Jong Soo, Lee Byung-Chul, Hwang Sung-Joo

College of Pharmacy, Chungnam National University

Various bupivacaine-loaded microspheres were prepared from poly(d,l-lactide) (PLA) and poly(d,l-lactic-co-glycolide) (PLGA) by a solvent evaporation method for the sustained release of drug. The effects of process conditions such as drug loading, polymer type and solvent type on the characteristics of microspheres were investigated. The prepared microspheres were characterized for their drug loading, size distribution, surface morphology and release kinetics. Drug loading efficiency and yield of PLGA microspheres were higher than those of PLA microspheres. The prepared microspheres had an average particle size below 5 ㎛. The particle size range of microspheres was 1.65~2.24 ㎛. As a result of SEM, the particle size of PLA microspheres was smaller than that of PLGA microspheres. In morphology studies, microspheres showed a spherical shape and smooth surface in all process conditions. In thermal analysis, bupivacaine-loaded microspheres showed no peaks originating from bupivacaine. This suggested that bupivacaine base in microspheres exist in an amorphous state. The release pattern of the drug from microspheres was evaluated for 96 hours. The initial burst release of bupivacaine base decreased with increasing the molecular weight of PLGA and the drug from microspheres released slowly. In conclusion, bupivacaine-loaded microspheres were successfully prepared from poly(d,l-lactide) and poly(d,l-lactic-co-glycolide) polymers with different molecular weights allowing control of the release rate.

[PE3-4] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Mono-, di-, and oligosaccharide analyses using HPAE/PAD and HPLC/fluorescence detector

Cho DueHyeon^{O}, Ryu ChangSoo, Kim HaHyung

College of Pharmacy, Chung-Ang University, Seoul 156-756, Korea

In the present study, we performed high-performance anion exchange chromatography using CarboPac PA-1 and CarboPac PA-100 columns with pulsed amperometric detector (HPAE/PAD) in order to quantitatively analyze mono-, di-, and oligosaccharides, including sialic acid derivatives such as N-acetylneuraminic acid, N-glycolylneuraminic acid and sialylated triantennary oligosaccharide. HPAE/PAD is an effective method for determining the composition and structure of carbohydrates without requiring any derivatization. HPAE/PAD analyses were performed using a BioLC system (Dionex). Elution was carried out in 16 mM NaOH for 0-20 min, and in 150 mM sodium acetate in 100 mM NaOH from 0-20 min for the analysis of sialic acid derivatives. A sensitive method for the structural analysis of sialylated oligosaccharide was also developed using HPLC with fluorescence detector. We are currently using our preliminary observations to analyze the structure and composition of oligosacchrides in our lab.

[PE3-5] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]