31PE-13

A METHOD FOR EVALUATING THE EFFECT OF DRUGS ON THE β-OXIDATION OF FATTY ACIDS BY LC-ESIMS/MS

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We have reported that nonsteroidal anti-inflammatory drugs (NSAIDs) and quinolone anti-microbial drugs (NQs) caused the perturbation in metabolism of fatty acids and glucose. Free fatty acids are known to impair insulin sensitivity. Insulin resistance is associated with an increase in inflammatory markers. The mechanism mediating insulin resistance is not completely understood. The first purpose is to elucidate the effect of drugs on the dynamic intracellular situation of free fatty acids and the acyl-CoAs involving in hepatic insulin resistance. Fatty acids were degraded by the acyl-CoA synthetases and four enzymes in the β-oxidation cycle. We developed a highly sensitive and specific method for evaluating the effect of drugs on the β-oxidation of fatty acids by LC-ESI-MS/MS. The reaction mixture consisted of the substrates (octanoic acid or palmitic acid), CoA, ATP, MgCl2, KCl, FAD, NAD+ and liver mitochondria in 0.2 M Tris-HCl buffer (pH 8.5). The each metabolite formed in the steps of fatty acid metabolism was well separated on a C18 reversed column using a linear gradient of ammonium acetate buffer (pH 5.3) – acetonitrile. The drugs tested (containing salicylic acid) exhibited the different mechanisms of inhibition of fatty acid metabolism. This method is very useful for the analysis for each metabolite produced in a series of fatty acid metabolism.

31PE-14

ESTIMATION OF BUSULFAN BIOAVAILABILITY IN CHILDREN UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION USING ORAL AND INTRAVENOUS POPULATION PHARMACOKINETIC PARAMETERS

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Busulfan is widely used for high-dose conditioning regimens before hematopoietic stem cell transplantation. Past reports indicated that young children have large apparent clearance (CL/F) and distribution volume (Vd/F), and the reason of these phenomenon were considered to be due to low bioavailability of young children. In this study, to estimate the change in bioavailability of busulfan with growth, we compared oral and intravenous population pharmacokinetic parameters in children. The age of patients treated with oral and intravenous busulfan were ranged 2-136 and 4-162 months, with median of 18 and 10 months, respectively. Using NONMEM analysis, oral and intravenous busulfan population pharmacokinetic parameters which considers the effect of age and body weight were obtained from 103 and 29 patients, with 1023 and 226 number of sampling, respectively. Then we simulated the changes in pharmacokinetic parameters after birth pursuant to the average growth curve of Japanese children by both of oral and intravenous population pharmacokinetic parameters. It was estimated that young children have a large Vd/F (L/kg) on oral administration, which declines precipitously up to the age of one year, and thereafter decreases slowly. On the other hand, Vd (L/kg) on intravenous administration was small at young children and increased with growth slowly. From these results, bioavailability of busulfan at the age of 4 months was estimated to be about 0.55, and thereafter increases to the 0.93 up to the age of 136 months.