2-P-73

PHARMACOKINETIC/PHARMACODYNAMIC MODELS OF ANTIHYPERTENSIVE DRUGS, NIFEDIPINE AND PROPRANOLOL, IN SPONTANEOUSLY HYPERTENSIVE RATS

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[Purpose] To examine the relationships between pharmacokinetic (PK) and changes in the blood pressures (BP), the heart rate (HR) and the QT intervals of antihypertensive drugs, nifedipine and propranolol, PK/pharmacodynamic (PD) models were conducted using spontaneously hypertensive rats (SHRs). Then the characteristics of these drugs in the body were investigated. [Methods] Male SHRs were anesthetized and a catheter was implanted in the carotid artery to monitor the BP. The HR and the QT interval were also continuously observed using electrocardiograph from -15 min to 90 min following initiation of the drug infusion. The iv infusion test solution containing propranolol (30.0 mg/kg) or nifedipine (2.0 mg/kg) was infused for 30 min from into the femoral vein. Blood samples were obtained up to 300 min and the plasma drug concentrations were measured by the LC/MS/MS method to estimate their plasma pharmacokinetics. The PK/PD analysis was applied to the data using Winnenlin⁶. [Results and Discussion] The change of the HR indicated clockwise hysteresis and the prolongation of the QT intervals indicated counterclockwise relationship between the plasma concentration and the effect in both drugs. So the compartmental PK model linked with PD model in which a hypothetical effect compartment was provided to describe a relationship between the PK and the response, and then PK and PD models were simultaneously analyzed. However, the BP change was more complicated than others and differed from one drug to another. In this case, the rapid BP alteration was induced following initiation of the drug infusion and the homeostatic mechanism should be taken the results into account in addition to the drug concentration dependent effect.

2-P-74

PHARMACOKINETICS AND TOXICODYNAMICS OF FLUOROQUINOLONES IN MICE

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Pharmacokinetic/Pharmacodynamic (PK/PD) analyses of fluoroquinolones have been extensively developed. Although their toxicity was reported, only few studies about Pharmacokinetic/Toxicodynamic (PK/TD) analysis have been reported. We previously showed that phototoxicity of lomefloxacin (LFLX) was well correlated with the area under the concentration-versus time curve (AUCuv) of LFLX in plasma during the long-wave ultraviolet light (UVA) irradiation. The objective of this study was to examine that the correlation was observed with other fluoroquinolones, such as sparfloxacin (SPFX) and levofloxacin (LVFX). SPFX (10, 30, 50 mg/kg) or LVFX (10,30,100 mg/kg) was administered to male ICR mice via iv bolus injection and exposed to UVA (1.5mW/cm²) for 4 h. An increase in ear thickness was measured to assess the drug-induced phototoxicity, and plasma samples were collected and analyzed to assess their pharmacokinetics. Both SPFX and LVFX exhibited linear disposition within the dose ranges used, which was well-characterized through the use of a two-compartment model. Ear thickness was monotonously increased for 96 h after the end of UVA irradiation. The ear thickness at 96 h was increased in a dose dependent manner, and this value was compared with PK parameters calculated from plasma concentration profiles. There was a high correlation between AUCuv and the ear thickness at 96 h. Intrinsic toxicity of the fluoroquinolones was defined by the ratio of the ear thickness to AUCuv followed the order of SPFX > LFLX > LVFX. The intrinsic toxicity of LFLX and SPFX was correlated with the reported in vitro cytotoxicity. The results of the present study indicate that the fluoroquinolone-induced phototoxicity can be predicted from the pharmacokinetic and toxicodynamic data and the prediction is applicable to clinical use of fluoroquinolones.