STUDY OF VARIOUS FACTORS AFFECTING BIODISTRIBUTION OF LIPOSOMES

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[Objective] In vivo efficacy of drug-containing liposome has been usually studied with animal model. But, most of these studies have been carried out without considering the influence of the animal model and the encapsulated drug in biodistribution of the liposome. This might mislead the in vivo efficiency of drug-containing liposomes. Various factors affecting the biodistribution of liposome must be considered in order to obtain liposomes with a superior pharmacological effect. Here, we examined the influence of 1) the mice genealogy, 2) the tumor inoculation and 3) the encapsulated drug (doxorubicin (DXR)), in the biodistribution of liposome. [Methods] Liposomes were composed of HEPC or EPC: Chol: mPEG2000-DSPE = 2:1:0.2 (mol/mol). Biodistribution of liposomes was determined on the basis of radioactivity of 3H-CHE, a lipid phase marker in the liposome. [Results and Discussion] In the mice genealogy (ddY, BALB/c and C57BL/6), there was no significant difference on the biodistribution of liposome. In the tumor-bearing mice, significant difference was observed in the accumulation of the liposome into tumor and spleen. In the tumor, the accumulated amount increased with increasing the size. Encapsulation of DXR significantly affected the biodistribution of the liposome; a reduction in the hepatic accumulation and an increase in the blood concentration were observed. Free DXR in empty liposome did not affect the biodistribution of the liposome. These results suggest that the DXR encapsulated in the liposome reduces the further uptake of the injected liposomes by the liver macrophages. In conclusion, in order to get the desired in vivo efficacy of drug-containing liposome, the biodistribution of liposomes with drug-containing formulation in animal model such as tumor-inoculated one may be necessary.

DEVELOPMENT AND EVALUATION OF NOVEL O/W EMULSION OF PACLITAXEL

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Paclitaxel (PTX) is a powerful chemotherapeutic agent against wide range of cancers, including ovarian, breast, head and neck, non-small cell lung and prostate cancers. Because of its poor water solubility, PTX is dissolved in the mixture of dehydrated ethanol and polyethoxylated castor oil (Cremophor EL) (1:1, v/v) for its clinical use. However, this formulation is associated with a number of pharmacological and pharmacokinetic concerns including the occurrence of serious hypersensitivity reactions to cancer patients. To overcome these problems, we tried to develop a safer formulation using o/w emulsion as a PTX vehicle. We prepared various o/w emulsions by using egg phosphatidylcholine, Tween 80 and the mixture of triglycerides with different lipid chain length as co-surfactant, surfactant and oil phase component, respectively. The mean particle diameters of emulsions prepared were around 130 nm. In-vitro anti-tumor activity was evaluated by intraperitoneal injection of emulsions to ascitic tumor bearing mice. It was found that the formulation containing tricaprin and triacetin (3:1, w/w, Emulsion D) significantly prolonged the life span. In-vitro release study showed that the release of PTX from Emulsion D was significantly faster than those from other preparations. In-vitro MTT assay also indicated that Emulsion D had the highest cytotoxicity, reflecting the fastest release of PTX from the formulation. These results indicate that the formulation with a potent in-vivo anti-tumor activity would have a favorable release profile and that Emulsion D would be the most effective. Now we are focusing on the evaluation of anti-tumor activity of PTX-loaded emulsion in a solid tumor mice model.