

**THE ACCELERATED CLEARANCE ON REPEATED INJECTION OF  
PEGYLATED LIPOSOMES IN RATS: LABORATORY AND  
HISTOPATHOLOGICAL STUDY**

TATSUHIRO ISHIDA<sup>1\*</sup>, RYUHEI MAEDA<sup>1</sup>, MASAKO ICHIHARA<sup>1</sup>,  
YASUKO MUKAI<sup>2</sup>, YOKO MOTOKI<sup>2</sup>, YOSHIE MANABE<sup>2</sup>, KENJI  
IRIMURA<sup>2</sup> and HIROSHI KIWADA<sup>1</sup>

<sup>1</sup>Department of Pharmacokinetics and Biopharmaceutics, The University of  
Tokushima, Tokushima 770-8505, Japan, <sup>2</sup>Drug Safety Research Laboratory,  
Taiho Pharmaceutical Co., Ltd., Tokushima 771-0194, Japan

PEGylated liposomes which have a long-circulating property have been expected as promising drug carriers in the DDS field. For clinical setting, the multiple injection of the liposomes should not be negligible. Limited number of data is available on the influence of multiple injection on their pharmacokinetics and the patients. In this study, the effect of repeated injection of PEGylated liposomes was examined with an animal model, rat. The first dose of intravenously administered PEGylated liposomes reduced the circulation half-life of the second subsequent dose as well as enhanced the hepatic accumulation of the second dose. The rapid clearance of the second dose, termed accelerated clearance effect (ACE), was strongly related to hepatic clearance of the second dose (CL<sub>h</sub>). When the interval was extended (more than 2 weeks), the effect was attenuated. In addition, when the third dose was injected at 4, 7 or 14 days after second injection (second dose was given at 5 weeks after first injection), the ACE became less pronounced. These results suggest that degree of the effect is affected by the extension of time-interval for serial injection. In the series of this study, the animals tolerated the repeatedly injected PEGylated liposomes with no change in general condition, body weight, hematology and serum chemistry. In addition, no histopathological change in liver and spleen and no significant complement consumption were detected. These results suggest that the multiple injection of the PEGylated liposomes do not give animal body a strong stimulation. The results obtained in this study have a considerable impact in and important implications on the clinical application, design and engineering of PEGylated liposomes for repeated intravenous administration.

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\*E-mail: ishida@ph.tokushima-u.ac.jp