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Accelerated blood clearance of PEGylated PLGA nanoparticles following repeated injections: Effects of polymer dose, PEG coating, and encapsulated etoposide in pre-administration

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Background and Aims: The present study was performed to investigate the accelerated blood clearance (ABC) induction upon repeated injections of PLGA-PEG nanoparticles (NPs) as a very commonly used drug carrier. The effect of polymer dose, PEG coating and encapsulated etoposide, as an anticancer drug, in the first injection on ABC phenomenon was also investigated. Furthermorethe production of anti-PEG IgM antibody was evaluated.
Methods: Etoposide loaded long-circulating PLGA-PEG NPs was developed by solvent evaporation method. Various pre-dose treatments, i.e. normal saline (as control), empty PLGA-PEG NPs at different polymer doses, empty PLGA NPs and etoposide loaded PLGA-PEG NPs were injected to male Wistar rats (13 groups). At the certain time intervals (3, 5, 7, 14 and 28 days) one dose of drug loaded PLGA-PEG NPs was injected as the second dose (hereafter test dose). At selected times blood samples were taken and plasma concentrations of etoposide were determined by a validated HPLC method. The anti-PEG IgM was also quantified.
Results : In the rats pre-administered with 100 µg of empty PLGA-PEG NPs at a timeinterval of 7 days, the value of the etoposide AUC for the test dose remarkably reduced ($p < 0.001$) and clearance was notably enhanced ($p < 0.00001$) compared to the control. This was accompanied by a significant anti-PEG IgM production. These results indicated the strong induction of ABC phenomenon by repeated injection of PLGA-PEG NPs. ABC was considerably altered by high polymer dose of first dose but encapsulated etoposide did not have any significant effect on ABC.
Conclusions: The results showed that the ABC phenomenon is induced by PLGA-PEG NPs due to anti-PEG antibody. Encapsulated etoposide did not alter the ABC effect, however, the dose schedule should be considered as an important factor in the design and therapeutic use of PLGA-PEG NPs for multiple drug therapy.

Keywords: Accelerated blood clearance (ABC); PLGA-PEG; Nanoparticles; Etoposide