PHARMACOKINETICS, BIODISTRIBUTION AND BIOAVAILABILITY OF LIPOSOMAL DRUGS

THERESA M. ALLEN*, G. CHARROIS and K. LAGINHA

Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada, T6G 2H7

Stealth liposomal doxorubicin (Doxil®/Caelyx®) passively targets to tumors through the enhanced permeability and retention (EPR) effect, which is a result of enhanced vascular permeability of tumor blood vessels. The endothelial lining of the diseased site contains gaps that can range from 380-780 nm which are large enough for the extravasation of liposomes (~100 nm). Once the liposomes are localized in the interstitial space, they are retained due to the impaired lymphatic drainage in solid tumors. Released (i.e., bioavailable) drug is able to diffuse into tumor cells where doxorubicin (DXR) exerts its anti-tumor effect. Several studies have measured the total drug delivered to tumors by liposomes. However, drug that remains sequestered in liposomes has no biological activity and measures of total tumor drug includes both encapsulated (i.e., non-bioavailable) drug and released (i.e., bioavailable) drug.

Few measurements of bioavailable drug levels have previously been attempted; we have now measured total and bioavailable drug levels in murine tumors using a new technique. When DXR is released from liposomes, a large amount of the released drug diffuses into the tumor nucleus where it binds to DNA, which functions as an irreversible sink for the drug; therefore nuclear DXR can, we propose, be used as a marker for bioavailable DXR. By measuring DXR bound to nuclear DNA in orthotopically implanted breast cancer tumors in vivo, we have attempted to determine the rate and extent of released (bioavailable) drug in tumor tissues for two formulations of liposomal DXR (slow and more rapid release rates) compared to free DXR. The bioavailability results have been correlated with therapeutic results found in the same model system for liposomes with different release rates. We hypothesize that the therapeutic efficacy of liposomal anticancer drugs can be significantly improved if the rate of bioavailability of drug from the carrier is optimized. In the same orthotopic breast cancer model we have also examined the effect of liposome size, drug release rate, dose, dosing schedule and dose intensity on the pharmacokinetics, tissue distribution, therapeutic effect and the ability to cause palmar plantar erythrodysesthesia (hand-foot syndrome).

In a xenograft model of human B lymphoma we have shown that drug release rate is an important determinant of doxorubicin-mediated toxicity. We have shown that anti-CD19-mediated targeting of liposomal DXR can significantly reduce the toxicity of intermediate-release formulations of liposomal DXR and

* E-mail: terry.allen@ualberta.ca
increase the therapeutic effect by altering the pharmacokinetics and biodistribution of the liposomal DXR. Studies such as these can improve our understanding of the relationships between the pharmacokinetics, biodistribution and physical parameters of liposomal drugs and can help in the rational design of improved liposomal carriers.