Title	Pharmacokinetic and Allometric Scaling Studies of Nanoparticle Formulations of Anthracyclines
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Abstract	Nanoparticle drug formulations have properties often substantially different from their small-molecule counterparts. The disposition of these nano-formulations, such as liposomes, is partially dictated by the composition of the carrier, thus altering the pharmacokinetic (PK) profile of the drug. An essential feature of the drug development process is selecting an appropriate starting dose for phase 1 clinical trials. PK analysis in preclinical animal models (*e.g.*, mice, rats, and dogs), followed by allometric scaling, plays a vital role in predicting PK of drug formulations in humans for this purpose. However, nano-formulations have had historical complications in accurately predicting human PK using standard allometric evaluation (*i.e.*, body weight-based). The current study evaluates the effects of PK modeling (non-compartmental versus compartmental analysis) and use of alternate physiologic parameters on allometric prediction of PK parameters (clearance, volume of distribution) of anthracyclines in different nano-formulations in humans. PK studies of four anthracycline formulations were performed at maximum tolerable dose in mice, rats, dogs, and humans: non-liposomal doxorubicin (Adriamycin®), PEGylated liposomal doxorubicin (Doxil®), non-PEGylated liposomal daunorubicin (DaunoXome®), and polymeric micellar doxorubicin (SP1049C). In addition to body weight, physiological parameters thought to be specifically relevant to nanoparticle clearance [*e.g.*, mononuclear phagocytic system (MPS) function and spleen blood flow] were used in allometric scaling to predict PK parameters in humans. Preliminary analyses indicate that MPS-related factors, including total monocyte count, baseline MPS function, and spleen/liver blood flow, provide the best correlation of PK properties of nano-formulations between species. Interestingly, clearance may be better predicted by compartmental analysis and/or the use of maximum lifespan potential (MLP), while volume of distribution is better predicted by non-compartmental analysis regardless of MLP. These results elucidate how non-standard application of allometric techniques may be necessary for nano-based agents compared to small-molecule drugs and guide improved dose selection of nano-formulations entering clinical trials.
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Conflicts of Interest	WC Zamboni holds equity in and licensed patent on a MPS probe.