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Pharmacokinetic Variability of Long-circulating Nanomaterials: Insights into its Origins and Neglected Importance in Rodent Models

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1. Introduction

- Interpatient variability in the pharmacokinetic behaviours of nanomaterial-based drug delivery systems is a common clinical observation.
- Pharmacokinetic variability can negatively impact pharmacodynamic endpoints such as efficacy and toxicity.
- Key sources of variability in nanomaterial pharmacokinetics are physicochemical characteristics (size, surface charge, etc.) and pathological changes affecting the function of monocytes.
- In preclinical nanomaterials research, pharmacokinetic variability is often obscured by experimental design and analytical approach.
- Proper preclinical characterisation of the origins and magnitude of pharmacokinetic variability with nanomaterials can improve predictive modelling of pharmacological effects in patients.

2. Study Objectives

i. Investigate the pharmacokinetic behaviours of long-circulating ~100-nm nanomaterials in rodents with varying experimental, material, and animal model factors (sex, immunodeficiency, etc).

ii. Characterise interanimal pharmacokinetic variability using machine learning analysis to identify the most predictive factors.

3. Materials & Methodology

Porphyrin-lipid containing nanoparticles (Porphysomes) were chosen as prototypical long-circulating nanomaterials. Porphysomes (University Health Network) are spherical, unilamellar nanovesicles ~100 nm in diameter and containing 55:40:5 mol/mol% porphyrin-phospholipid conjugate:Cholesterol:DSPE-MPEG$_{2000}$. Male and female BALB/cAnNHsd and Hsd:Athymic Nude-Foxn1^{nu} mice (Envigo) were reused in 2~3 independent pharmacokinetic experiments, separated by a 4-week washout period. Intravascular Porphysome administration was performed as bolus injections of ~200 µL via the tail vein. Non-invasive serial blood sampling was performed in individual animals from the saphenous vein and the plasma concentration of Porphysomes assessed with fluorescence spectroscopy (1.0 mg/L L.O.D.). Noncompartment pharmacokinetic analysis (NCA) and unsupervised learning (or cluster) analysis were performed with MATLAB R2020a.

4. Analysis of the Factors Affecting Nanomaterial PK in Mice with Machine Learning

Experimental Factors:
Dose-level

- Linear PK range (1~20 mg/kg)
- Nolinear PK range
- Cluster analysis results

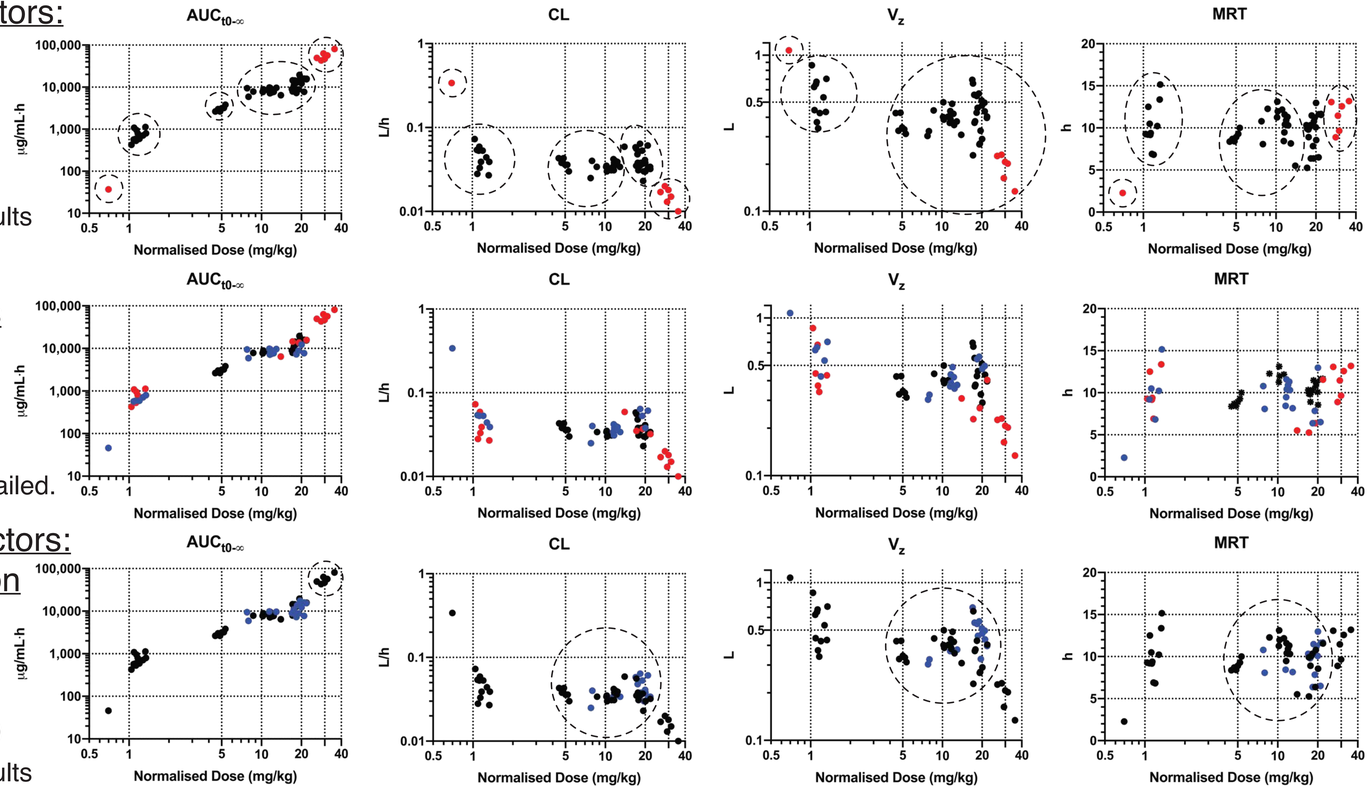
Material Factors:
Batch Differences

- Batch 1 (*dia.* 100-nm)
- Batch 2 (*dia.* 97-nm)
- Batch 3 (*dia.* 106-nm)

N.B. Cluster analysis failed.

Animal Model Factors:
Monocyte Function

- Immunocompetent (BALB/c mice)
- Immunodeficient (Athymic nude mice)
- Cluster analysis results



5. Interpretation of Factors Affecting PK

- Significant interanimal variability can be appreciated in the pharmacokinetic parameters (AUC, CL, V_z, MRT) of individual animals at equivalent nanomaterial dose-levels.
- Preliminary analysis of individual pharmacokinetics parameters with unsupervised learning (cluster analysis) identified only ***dose-level*** as a predictive factor for pharmacokinetic variability in the current dataset.

6. Conclusions

- Pharmacokinetic parameters AUC/dose, CL and V_z appear best suited for identifying and evaluating nanomaterial pharmacokinetic variability in rodents.
- Dose-level was identified in the current dataset as the main factor leading to pharmacokinetic variability, but not batch differences nor monocyte function.
- Alternative analytical approaches (e.g., supervised learning) or additional feature engineering may be required to identify other predictive factors.