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Drug Metabolism and Buffer Behaviour in Paediatrics in Relation to Birth Exposure

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Abstract

Although pediatric drug development has progressed over the past decades, off-label use of adult pediatric drugs remains a significant clinical problem. Nano-based drugs are important drug delivery systems that can improve the bioavailability of various therapeutics. However, the use of nanobased drugs for use in the pediatric population is challenged by the lack of pharmacokinetic (PK) data in this population. To fill this data gap, we examined the PK of polymer-based nanoparticles in term-equivalent neonatal rats. It is a polymeric nanoparticle that has been extensively studied in adult populations but less commonly used in neonates and children. We quantified the PK parameters and biodistribution of PLGA-PEG nanoparticles in period-equivalent healthy rats, demonstrating the PK and biodistribution of polymeric nanoparticles in neonatal rats. We further investigated the effects of surfactants used to stabilize PLGA-PEG particles on PK and biodistribution. The nanoparticles showed the highest accumulation in serum 4 hours after intraperitoneal injection, 54.0% of the injected dose for particles containing Pluronic® F127 (F127) as a stabilizer and 54.0% for particles containing poloxamer 188 (P80) as a stabilizer. 54.6% of the dose.) as a stabilizer. The half-life of PLGA-PEG particles loaded with F127 was 5.9 hours, which was significantly longer than the half-life of 1.7 hours for PLGA-PEG particles loaded with P80. Among all organs, liver showed the highest accumulation of nanoparticles. Twenty-four hours after dosing, the accumulation of PLGA-PEG particles in the F127 formulation was 26.2% of the injected dose, and the accumulation of particles in the P80 Less than 1% of injected nanoparticles were observed in healthy rat brains for F127 and P80 formulated particles. These PK data inform the application of polymeric nanoparticles in neonates and provide a basis for the transfer of polymeric nanoparticles for drug delivery in the pediatric population.

Keywords: Nanomedicine; Pediatrics; Drug delivery; Half-life; Nanoparticle accumulation; Clinical translation

Introduction

Over the past decades, the Food and Drug Administration (FDA) has encouraged the development of formulations for the pediatric population. In particular, the Pediatric Formulations Initiative, both based in the United States and Europe is making efforts to explore nanomedicine-based formulations for children. Nanomedicine has exploded in development over the past three decades and has become a promising therapeutic platform for the pediatric population [1]. In addition to enhancing therapeutic efficacy, nanomedicine can mask drug taste, improve drug bioavailability and permeability, and reduce off-site or off-target toxicity in children. Currently, most nanomedicine platforms are either preclinically evaluated in adult models or clinically evaluated in adults, and off-label use of adult drugs in pediatrics remains a significant clinical problem [2]. Although the original purpose of off-label use is to help these patients, off-label use of medicines can put children, especially newborns, infants, and children under 2 years of age, at risk of adverse drug reactions [3].

The development of nanomedicine for pediatrics is an even more important data gap for neonates due to the lack of pharmacokinetic (PK) data in the pediatric population, limited patient numbers and the technical and ethical implications of clinical trials in this population is challenged by Even established nanoparticle platforms such as liposomes and polymersomes have limited PK data in pediatric and neonatal populations. To fill this data gap, we attempted to generate PK data in a neonatal model of polymeric nanoparticles [4].

As one of the most commonly used polymeric nanoparticles, poly (lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) nanoparticles have been shown to enhance the physico-chemical and PK properties of cargoes, thereby enhancing drug delivery plays important roles in delivery PLGA-based formulations are approved for multiple biomedical uses; PLGA-based nanoformulations are highly biocompatible and have been extensively studied in adults. Therefore, there may be significant benefits when used in children, including newborns [5].

We also investigated the effects on PK parameters and biodistribution when surfactants were used as stabilizers in the formulation process. Previous studies have shown that surfactants used in the emulsification process influence the biodistribution of polymeric nanoparticles, but the effect of surfactants on pediatric PK is unknown. We selected Pluronic® F127 (F127) surfactant from the Pluronic surfactant family and Tween 80 (P80) from the polysorbate surfactant family to produce PLGA-PEG nanoparticles with similar particle size and zeta potential [6]. These surfactants are nonionic surfactants and are most commonly used in nanomedicine due to their lower toxicity compared to ionic surfactants. Furthermore, among nonionic surfactants, most nanoformulations contain polysorbate, poly (vinyl alcohol) or Pluronics® as stabilizers, highlighting their frequent use in the literature. Previous literature also reported that nanoparticles loaded with polysorbate 80 (P80) have a higher affinity for circulating apolipoprotein E (ApoE), which is associated with greater crossing of the blood-brain barrier (BBB). Associated with improved targeting in the brain through penetration. The difficulty of therapeutic agents in crossing the BBB has led to an increasing focus on targeting the brain. Therefore, in this study, we

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further focused on the effect of surfactant on the PK, biodistribution and cell association of PLGA-PEG nanoparticles in terms of brain equivalents [7].

Our main results provide basic PK data in term-equivalent rats that can be used to build physiologically-based pharmacokinetic (PBPK) or similar models to support first-human predictions in neonates. Our results also provide guidance on the design and delivery of therapeutic polymeric nanoparticles for use in the neonatal population [8].

Immunohistochemistry

To characterize the biodistribution at the tissue level, one hemisphere of the brain, each part of the lung and liver, and one kidney were placed on gradients from formalin to 30% sucrose and sectioned at 30 μm on a Leica cryostat. I made frozen sections. To assess brain distribution, primary antibodies against microglia (1:250 rabbit anti-Iba1, Wako, Fujifilm, Minato, Tokyo, Japan) and neurons (1: 250 Donkey Anti-NeuN, Abcam, Cambridge, UK) was prepared in 1x PBS containing 1% Triton X-100 (Sigma-Aldrich) and 3% normal goat serum (Sigma-Aldrich). A primary antibody solution was added to the tissue sections and left for 4-6 hours at room temperature in a humidified dark room. Tissue sections were washed twice with 1X PBS. Secondary antibodies were dissolved in 1x PBS containing 1% Triton X-100 and added to tissue sections and incubated for 2 hours [9].

Results

Characterization and stability of cf647-labeled nanoparticles

CF647-labeled PLGA-PEG nanoparticles were formulated with 1.27% surfactant and 1% P80 surfactant by standard nanoprecipitation method. After formulation, hydrodynamic size, PDI and zeta potential were measured using DLS and Zetasizer. The stability of CF647 dye-tagged nanoparticles was verified indirectly due to the limited ability to directly visualize polymeric nanoparticles in tissue samples. CF647 free dye detected by absorbance at 650 nm showed an absorbance peak at 650 nm. Blank serum samples showed no absorbance signal at 650 nm. Injection of extracts PLGA-PEG/F127 and PLGA-PEG/P80 nanoparticles showed no absorbance peaks, serum injection after intraperitoneal administration [10].

Discussion

When comparing the action of surfactants, it is necessary to control the physicochemical properties of the nanoparticles. In this study, both PLGA-PEG/F127 and PLGA-PEG/P80 were formulated to produce particles in the size range of 60–70 nm, 0.2 PDI, near-neutral zeta potential, and under physical conditions. Reduced the impact of differences. Four hours after injection, PLGA-PEG/F127 and PLGA-PEG/P80 had similar time delays before entering the systemic circulation, with a rapid increase in serum concentrations starting at 1 hour and reaching peak concentrations after 4 hours. The biodistribution of nanoformulations can be affected by their surface functionality, composition, surface charge, and particle shape, whereas nanoparticle size is critical for nanoparticle biodistribution. With a nanoparticle size difference of 20 nm, the percentage injection dose in serum can vary. In general, smaller nanoparticles take less time to be absorbed from the peritoneal cavity into the systemic circulation, resulting in higher bioavailability but shorter exposure times compared to larger nanoparticles. I'm here. P80 is said to have a high affinity with ApoE. Therefore, a possible explanation for the different profiles is that the protein composition of coronas adsorbed on PLGA-PEG/P80 is different from that of PLGA-PEG/F127. I'm here. -PEG/P80). Regarding serum half-life and bioavailability, PLGA-PEG/F127 may increase systemic circulation time compared to PLGA-PEG/P80, which may increase the dosing interval.

Conclusions

PLGA-PEG nanoparticles show promise as drug delivery vehicles to the neonatal population. PK data can guide dosage decisions to improve nanoparticle biodistribution in neonates. In this study, we demonstrated that PLGA-PEG nanoparticles formulated with different surfactants exhibited different PK parameters and biodistribution at the systemic and organ level. Compared to PLGA-PEG/P80, PLGA-PEG/F127 had a longer systemic circulation time and higher bioavailability, resulting in longer half-lives in heart, lung, spleen, kidney, and brain. In the brain, PLGA-PEG/P80 showed better distribution in the brain parenchyma, whereas PLGA-PEG/F127 maintained association with brain capillaries, although both formulations accumulated less in the brain. The neonatal population is underrepresented in clinical PK studies, resulting in data gaps that are a major cause of off-label drug use in neonates. Understanding the PK profile, biodistribution, and associated residence time of PLGA-PEG and other polymeric nanoparticles in neonates will aid in the design and implementation of therapeutic nanoparticles with maximum efficacy and minimum toxicity.

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