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Nanomedicines in the future of pediatric therapy☆

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ABSTRACT

Nanotechnology has become a key tool to overcome the main (bio)pharmaceutical drawbacks of drugs and to enable their passive or active targeting to specific cells and tissues. Pediatric therapies usually rely on the previous clinical experience in adults. However, there exists scientific evidence that drug pharmacokinetics and pharmacodynamics in children differ from those in adults. For example, the interaction of specific drugs with their target receptors undergoes changes over the maturation of the different organs and systems. A similar phenomenon is observed for toxicity and adverse effects. Thus, it is clear that the treatment of disease in children cannot be simplified to the direct adjustment of the dose to the body weight/surface. In this context, the implementation of innovative technologies (e.g., nanotechnology) in the pediatric population becomes extremely challenging. The present article overviews the different attempts to use nanotechnology to treat diseases in the pediatric population. Due to the relevance, though limited available literature on the matter, we initially describe from preliminary in vitro studies to preclinical and clinical trials aiming to treat pediatric infectious diseases and pediatric solid tumors by means of nanotechnology. Then, the perspectives of pediatric nanomedicine are discussed.

Contents

Abbreviations: ACTs, artemisinin combined therapies; ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; ARV, antiretrovirals; AUC, area-under-the-curve; BMS, burning mouth syndrome; CD, cytosine deaminase; CNS, central nervous system; CPT, camptothecin; DCL, drug-in-CD-in-liposome; DDS, drug delivery systems; DOTS, Directly Observed Treatment, Short Course; EFV, efavirenz; EMA, European Medicines Agency; EPR, enhanced permeation and retention; EuPFI, European Paediatric Formulation Initiative; EWS, Ewing sarcoma; 5-FC, 5-fluorocytosine; FDAMA, Food and Drug Administration Modernization Act; FDCs, fixed dose combinations; FP7, Seventh Framework Programme; Gal, galactose; GD2, disialogangloside; GRIP, Global Research in Paediatrics – Network of Excellence; HER2, human epidermal growth factor receptor-2; HIV/AIDS, human immunodeficiency virus/acquired Immunodeficiency syndrome; HPMA, *N*-(2-hydropropyl)methacrylamide copolymer; INH, isoniazid; i.v, intravenous; LRP, lung resistance protein; Man, mannose; MCT, medium-chain triglyceride; MDM2, murin double minute; MDR, multidrug-resistance; miRNAs, microRNAs; MRI, magnetic resonance imaging; MRP-1, multidrug resistance protein-1; MSN, mesoporous nanoparticles; MTP, muramyl tripeptide; Nano-DDS, nano-drug delivery system; NCAMs, neural cell adhesion molecules; NIR, near infrared; NSC, neural stem cell; PDT, photodynamic therapy; PEG, poly(ethylene glycol); PEO-PPO, poly(ethylene oxide)-*b*-poly(propylene oxide) block copolymer; PIP, pediatric investigation plan; PLGA, poly(lactide-co-glycolide); PM, polymeric micelles; PRD, poverty-related diseases; RGD, Arg-Gly-Asp; R&D, research and development; RIF, rifampicin; siRNA, interference RNA; TB, tuberculosis; US-FDA, US Food and Drug Administration; WHO, World Health Organization.

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1. Introduction

Nanotechnology has become a key tool to overcome fundamental (bio)pharmaceutical drawbacks of drugs such as poor aqueous solubility, low physicochemical stability and insufficient bioavailability [1–3]. Nano-drug delivery systems (nano-DDS) enable the passive or active targeting of the payload to specific cells and tissues, increasing its accumulation in the action body site and reducing adverse effects by decreasing systemic exposure to the free/active drug [4,5]. Additionally, nanotechnology has been shown to improve localized drug delivery by alternative administration routes (e.g., inhalation) in organs protected by anatomical or physiological barriers, such as the central nervous system. Irrespective of the level of complexity, the potential of nanomedicine to improve the diagnosis and the treatment of disease has been extensively documented. Thus, regardless of the regulatory demands, a reasonable number of nanomedicines have already made their way to the market [6,7]. However, all of them are for use in adults.

Because traditionally the development of pediatric treatments usually relied on the previous experience in adults, which is still scarce for most nanotechnology platforms, there do not exist approved pediatric nanomedicines yet. The application of new regulatory initiatives, such as the pediatric investigation plan (PIP) promoting specific studies in children to obtain the necessary data (efficacy and toxicity, when it is safe to do so) for the approval of a new pharmaceutical product will facilitate the authorization of medicines for children.

Children present biological and/or metabolic differences with respect to adults due to the gradual development and maturation of the different organs and systems after birth [8,9]. Thus, in the case of diseases that hit both adults and children, nanomedicines need to be primarily adjusted to fit the pediatric use, a process that might demand the development of a different pharmaceutical formulation, and then clinically trialed in children. Furthermore, in the case of diseases that are children-specific or that show substantially greater morbidity in children, nanomedicines need to be especially developed [10]. These facts regretfully enter into conflict with the complexities of the fragmented pediatric market and the challenging pediatric clinical trials that discourage researchers in both academia and industry to investigate pediatric nano-DDS.

The present article overviews the different attempts to use nanotechnology to treat diseases in children. Due to the relevance, though limited available literature on the matter, we initially describe from preliminary in vitro studies to preclinical and clinical trials aiming to treat pediatric infectious diseases and solid cancers by means of nanotechnology. Then, the perspectives of pediatric nanomedicine are discussed.

2. Challenges of the pediatric population

There exists global consensus among clinicians that children are not just small adults [11,12]. This statement is not a demagogic cliché but it is based on scientific evidence showing that children present differences in drug absorption, biodistribution, metabolism and excretion with respect to adults [13]. Also, derived from the differential interaction of drugs with their cellular targets, children show differences in pharmacodynamics [14–16]. In this context, it is crystal clear that the treatment of disease in children cannot be simplified to the direct adjustment of the dose to the body weight/surface [17].

An additional point of consideration is that based on differences in biology and metabolism, the pediatric subpopulation is sub-classified into subgroups, namely preterm newborn infants, term newborn infants (0–27 days), infants and toddlers (28 days-23 months), preschool children (2–5 years), school children (6–11 years) and adolescents (12–16/18 years) [9,18]. Each sub-category shows different gastrointestinal pH and transit, intestinal motility and conjugation and transport of bile salts [8,19]. Also, the level of cognitive development could impact formulation appropriateness (e.g., in the case of inhalatory products) [20] and the feasibility of clinical trials [21–23]. For instance, clinical trials in children are more complicated due to scientific, clinical, ethical, technical and logistical challenges, that have discouraged the process over the years [24–27]. Furthermore, toxicological aspects of the exposure to nanoparticles should be thoroughly assessed, especially by inhalation, because children show increased particle deposition in the lungs with respect to adults [28]. For example, the biocompatibility of several liposome formulations is well-known and a few nano-DDS have reached the clinical phase in adults [29,30]. However, information regarding their safety in children is very limited. Other platforms such as carbon nanotubes are more controversial and their clinical use seems less likely [31]. All these facts converge to reduce the flexibility and the proxfitability of the fragmented pediatric market and position children at the top of the vulnerability scale [32,33].

3. Infectious diseases

Despite the availability of a broad spectrum of antibiotics, the treatment of infections has become an increasing challenge of modern medicine due to the emergence of resistant pathogens. The situation is more critical in poverty-related diseases (PRDs) and even more in the case of the pediatric population owing to the reasons mentioned above. In advance the incipient progresses made at the interface of nanomedicine and the therapy of pediatric HIV, TB and malaria, three infections that claim the largest number of lives every year, will be overviewed [34].

3.1. HIV/AIDS

HIV/AIDS is the most lethal infection of our times with approximately 2.5 million annual deaths [35]. The number of antiretrovirals (ARVs) approved for pediatric administration is smaller than the one for adults and pharmacokinetic data are more limited due to the complexity of the clinical trials [36,37]. Additional drawbacks are the lack of certified liquid (e.g., solutions and suspensions), chewable [38], dispersible [39–41] and orodispersible formulations [42–44] that ease dose adjustment and ingestion and the development of pediatric fixed dose combinations (FDCs) [45,46]. Regardless of the strategy of choice, the production process should be counterbalanced to maintain medication costs under limits that ensure patient affordability [47,48]. The disease hits both the adult and the pediatric population and, thus the development of anti-HIV nanomedicines could be beneficial for all the patient sub-populations. Nevertheless, the number of research works aiming to develop nanotechnology-based anti-HIV medicines in general and for children in particular is remarkably scarce.

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