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Nanostructured Lipid Carriers for Artemisinin Delivery: Overcoming Resistance in Severe Pediatric Malaria

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ABSTRACT

Severe pediatric malaria remained a leading cause of morbidity and mortality in sub–Saharan Africa and parts of Southeast Asia, despite widespread deployment of artemisinin-based combination therapies. Artemisinin derivatives acted rapidly against *Plasmodium falciparum*, yet emerging resistance associated with parasite stress response pathways and Kelch13 mutations threatens their sustained clinical efficacy, particularly in vulnerable pediatric populations with altered pharmacokinetic profiles. This review examined the potential of nanostructured lipid carriers as advanced delivery systems to enhance artemisinin bioavailability, stability, and therapeutic performance in severe childhood malaria. The article was developed through a critical synthesis of contemporary literature spanning malaria pathophysiology, pharmacology of artemisinin, nanocarrier engineering, and translational pediatric therapeutics. Evidence indicated that nanostructured lipid carriers improved drug solubility, prolonged systemic circulation, enabled controlled release, and enhanced intracellular accumulation within parasitized erythrocytes, thereby potentially mitigating mechanisms of partial resistance. Furthermore, these systems offered opportunities for dose optimization and combination therapy while maintaining favorable safety profiles. Nanostructured lipid carriers represented a promising strategy to restore and sustain artemisinin efficacy in severe pediatric malaria, and targeted translational research is warranted to accelerate clinical implementation.

Keywords: Severe pediatric malaria, Artemisinin resistance, Nanostructured lipid carriers, Drug delivery systems, Plasmodium falciparum.

INTRODUCTION

Malaria continues to impose a profound global health burden, with children under five years bearing a disproportionate share of mortality [1, 2]. Severe pediatric malaria, primarily caused by *Plasmodium falciparum*, manifests as cerebral malaria, severe anemia, metabolic acidosis, and multiorgan dysfunction. Despite significant advances in vector control and pharmacotherapy, the disease remains a major contributor to preventable childhood deaths in endemic regions. Artemisinin and its derivatives revolutionized malaria treatment owing to their rapid parasiticidal action and ability to reduce parasite biomass swiftly [3]. However, the emergence of artemisinin resistance, particularly in Southeast Asia and increasingly in parts of Africa, threatens to reverse these gains.

Resistance is characterized by delayed parasite clearance and is associated with mutations in the Kelch13 propeller domain and adaptive stress response pathways within the parasite [4]. Compounding this challenge are the pharmacokinetic limitations of artemisinin compounds, including poor aqueous solubility, short half-life, and variable bioavailability in pediatric patients. These factors compromise therapeutic exposure and may facilitate selection of partially resistant parasite populations.

Nanostructured lipid carriers have emerged as an advanced drug delivery platform capable of enhancing solubility, stability, and controlled release of lipophilic compounds [5]. By optimizing pharmacokinetic behavior and facilitating targeted intracellular delivery, these systems offer a promising strategy to improve therapeutic outcomes in severe pediatric malaria [6]. This review explores the molecular basis of severe malaria and artemisinin resistance, delineates pharmacological challenges in children, examines the design and mechanistic advantages of

nanostructured lipid carriers, evaluates their potential to overcome resistance, and discusses translational and clinical perspectives. The purpose of this article is to provide a mechanistically grounded and clinically relevant analysis of how nanostructured lipid carriers may restore and sustain artemisinin efficacy in severe pediatric malaria.

Molecular Pathophysiology of Severe Pediatric Malaria and Mechanisms of Artemisinin Resistance

Severe pediatric malaria represents a complex interplay between parasite virulence factors and host inflammatory responses [7]. Following hepatic maturation, *Plasmodium falciparum* invades erythrocytes, where it digests hemoglobin within the acidic digestive vacuole. This process releases free heme, which is detoxified into hemozoin. Artemisinin derivatives exert their activity through cleavage of the endoperoxide bridge in the presence of ferrous iron derived from heme metabolism, generating reactive oxygen species and carbon-centered radicals that damage parasite proteins and membranes [8].

In children, high parasite biomass and immature immune regulation contribute to exaggerated inflammatory responses [9]. Sequestration of infected erythrocytes in cerebral microvasculature leads to endothelial activation, blood-brain barrier dysfunction, and neurological complications. Severe anemia arises from hemolysis and impaired erythropoiesis, while metabolic acidosis reflects systemic hypoxia and lactate accumulation.

Artemisinin resistance does not typically manifest as classical treatment failure but rather as delayed parasite clearance. Mutations in the Kelch13 gene are associated with altered parasite stress responses, including enhanced unfolded protein response pathways and quiescence during early ring stages [10]. This adaptive dormancy allows parasites to survive transient drug exposure. Furthermore, reduced hemoglobin uptake and altered redox balance may decrease activation of the artemisinin endoperoxide bridge, attenuating cytotoxicity.

Subtherapeutic drug concentrations, especially in pediatric populations with variable absorption and metabolism, create a permissive environment for survival of partially resistant parasites. Thus, overcoming resistance requires strategies that ensure sustained therapeutic concentrations and effective intracellular drug delivery.

Pharmacokinetic and Biopharmaceutical Challenges of Artemisinin in Children

Artemisinin and its derivatives, including artesunate and artemether, are characterized by limited aqueous solubility and chemical instability under physiological conditions [11]. Rapid hepatic metabolism, primarily via cytochrome P450 enzymes, results in short elimination half-lives. Consequently, therapeutic efficacy depends on combination regimens and repeated dosing schedules.

In pediatric patients, pharmacokinetic variability is pronounced due to developmental differences in hepatic enzyme expression, body composition, plasma protein binding, and gastrointestinal absorption [12]. Severe malaria itself may impair drug absorption through vomiting, reduced gut perfusion, and altered metabolic capacity. These factors may lead to inconsistent plasma concentrations and reduced exposure to active metabolites.

The lipophilic nature of artemisinin compounds poses formulation challenges. Conventional oral and parenteral formulations may exhibit erratic bioavailability. Intravenous artesunate remains the standard for severe malaria [13]; however, maintaining optimal therapeutic levels remains critical to prevent recrudescence and resistance selection.

Poor stability and rapid clearance necessitate frequent dosing, which may compromise adherence in resource-limited settings. Furthermore, insufficient intracellular accumulation within infected erythrocytes may reduce drug efficacy against ring-stage parasites exhibiting stress-induced quiescence [14].

Addressing these limitations requires innovative delivery systems capable of enhancing solubility, prolonging circulation time, protecting the drug from premature degradation, and facilitating targeted intracellular delivery. Nanostructured lipid carriers provide a rational and mechanistically informed approach to meet these pharmacological demands.

Nanostructured Lipid Carriers: Composition, Design Principles, and Mechanistic Advantages

Nanostructured lipid carriers are advanced lipid-based nanocarriers composed of a blend of solid lipids and liquid lipids stabilized by surfactants [15]. Unlike solid lipid nanoparticles, which consist solely of crystalline solid lipids, nanostructured lipid carriers incorporate liquid lipid fractions that create imperfections within the crystalline matrix. These structural imperfections enhance drug loading capacity and reduce expulsion during storage.

The lipid matrix typically includes physiologically compatible lipids such as glyceryl monostearate combined with medium-chain triglycerides. Surfactants such as polysorbates stabilize the nanoscale dispersion and prevent aggregation. Particle sizes generally range from 50 to 300 nanometers, facilitating cellular uptake and enhanced permeability [16].

Drug incorporation occurs through solubilization within the lipid matrix, allowing entrapment of lipophilic compounds such as artemisinin derivatives. Controlled release profiles can be engineered by adjusting lipid composition and crystallinity. The nanometric size promotes enhanced absorption across biological membranes and improved biodistribution.

Mechanistically, nanostructured lipid carriers protect encapsulated drugs from hydrolytic and oxidative degradation [17-23]. They can prolong systemic circulation and enable sustained release, maintaining therapeutic

concentrations over extended periods. Furthermore, lipid-based carriers may facilitate fusion with cellular membranes, enhancing intracellular drug delivery to parasitized erythrocytes.

From a translational perspective, these systems are amenable to scalable manufacturing methods, including high-pressure homogenization. Biocompatibility and reduced systemic toxicity further strengthen their appeal for pediatric applications.

Mechanisms by Which Nanostructured Lipid Carriers May Overcome Artemisinin Resistance

Nanostructured lipid carriers offer multiple mechanistic pathways to counteract artemisinin resistance. First, enhanced solubility and bioavailability increase systemic drug exposure, reducing the likelihood of subtherapeutic concentrations that permit parasite survival [18,24-28]. Sustained release kinetics maintain effective levels during critical ring stage development.

Second, improved intracellular delivery may enhance drug accumulation within infected erythrocytes. Lipid-based nanoparticles can interact with erythrocyte membranes and potentially exploit parasite-induced permeability pathways, facilitating entry into the intracellular parasite niche [19,29-32]. Higher local concentrations may overcome partial resistance associated with stress-induced quiescence.

Third, protection from premature metabolism and degradation preserves active drug integrity. Encapsulation may shield artemisinin from rapid hepatic biotransformation, extending effective half-life. This pharmacokinetic optimization reduces selection pressure associated with fluctuating drug levels.

Fourth, nanostructured lipid carriers enable co-delivery of artemisinin with partner drugs or adjuvants within a single carrier system [20,33-35]. Such combination strategies may target complementary pathways, reducing the probability of resistance amplification.

Collectively, these mechanisms suggest that nanostructured lipid carriers can restore pharmacodynamic potency by aligning drug exposure with parasite vulnerability windows, thereby addressing both biochemical and pharmacokinetic contributors to resistance.

Translational and Clinical Perspectives in Pediatric Malaria Therapy

Preclinical investigations have demonstrated improved antimalarial efficacy of lipid-based nanocarriers in vitro and in animal models. Enhanced parasite clearance rates and prolonged survival have been observed relative to conventional formulations. Toxicological studies generally indicate favorable safety profiles, attributable to the use of biodegradable lipids [21,36-39].

In pediatric populations, safety is paramount. Lipid excipients must be carefully selected to avoid immunogenicity or metabolic disturbances. Dosing strategies require optimization to account for age-dependent pharmacokinetics. Regulatory approval will necessitate rigorous evaluation of stability, scalability, and quality control parameters.

Manufacturing considerations include cost-effectiveness and adaptability to resource-constrained settings where malaria burden is highest [22,40-43]. Advances in scalable homogenization technologies and stable dry powder formulations may facilitate broader implementation.

Future research should integrate pharmacokinetic modeling, mechanistic studies of intracellular delivery, and well-designed clinical trials in children with severe malaria. Collaboration between nanotechnologists, pharmacologists, and clinicians will be essential to translate promising preclinical findings into clinical benefit [23].

CONCLUSION

Severe pediatric malaria remains a life-threatening condition compounded by the emergence of artemisinin resistance and the pharmacokinetic vulnerabilities inherent in childhood physiology. Artemisinin derivatives, while highly potent, are constrained by poor solubility, rapid metabolism, and limited duration of therapeutic exposure. Resistance mechanisms rooted in parasite stress adaptation and Kelch13-associated mutations further diminish treatment efficacy. Nanostructured lipid carriers provide a scientifically compelling solution by enhancing drug solubility, stabilizing active compounds, prolonging systemic circulation, and facilitating intracellular delivery to infected erythrocytes. Through sustained therapeutic concentrations and improved pharmacodynamic alignment, these nanocarriers have the potential to mitigate partial resistance and improve clinical outcomes in severe pediatric malaria. Moreover, their capacity for combination drug loading offers strategic advantages in integrated antimalarial therapy. Continued translational research, supported by rigorous pharmacological and clinical evaluation, is required to fully realize their therapeutic promise. Strategic investment in clinically oriented research on nanostructured lipid carrier-based artemisinin formulations should be prioritized to strengthen therapeutic resilience against resistance in severe pediatric malaria.

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