A Safety And Dose-Escalation Study Of Zinc Supplementation In Pediatric Critical Illness

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Synopsis:
Our recently published studies in children with septic shock demonstrated that pediatric septic shock is characterized by large scale repression of genes that either directly depend on normal zinc homeostasis or directly participate in zinc homeostasis. Functional validation studies demonstrated that nonsurvivors of pediatric septic shock have abnormally low serum zinc concentrations. A follow-up pilot study in a general population of critically ill children demonstrated that the presence of low plasma zinc concentrations is a prevalent problem in critically ill children. In addition, low plasma zinc concentrations correlate inversely with indices of inflammation and directly with the number of organ failures. These preliminary data, coupled with the expected safety of zinc supplementation, provided the rationale for a double blinded, prospective, placebo-controlled trial of zinc supplementation in critically ill children, with the two primary study endpoints to assess efficacy being highly clinically relevant: reduction of the lymphopenia rate and improvement of glucose homeostasis. Although the proposal was well-received, the primary concern precluding funding of this trial were lack of safety and dosing data for intravenous zinc. We have therefore developed a proposal for a Phase I/II study of safety and pharmacokinetics to address these concerns. It is anticipated that data generated through this proposal will provide the necessary preliminary data to re-submit our application for an interventional efficacy trial of zinc supplementation in critically ill children.