Zinc or Albendazole Attenuates the Progression of Environmental Enteropathy: A Randomized Controlled Trial

Kelsey N. Ryan,[*] Kevin B. Stephenson,[*] Indi Trehan,[*,‡] Robert J. Shulman,[§] Chrissie Thakwalakwa,[‖] Ellen Murray,[*] Kenneth Maleta,[‖] and Mark J. Manary[*,§,‖]

*Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri; ‡Department of Paediatrics and Child Health, ‖Department of Community Health, University of Malawi College of Medicine, Blantyre, Malawi; and §Children's Nutrition Research Center, Baylor College of Medicine, Houston, Texas

BACKGROUND & AIMS: **Environmental enteropathy (EE) is a subclinical condition among children in the developing world, characterized by T-cell infiltration of the small-bowel mucosa and diffuse villous atrophy. EE leads to macronutrient and micronutrient malabsorption and stunting, with a resultant increased risk for infection and reduced cognitive development. We tested the hypothesis that zinc and albendazole treatments would reduce the severity of EE in rural African children.**

METHODS: **In a randomized, double-blind, placebo-controlled trial in rural southern Malawi, asymptomatic children, 1 to 3 years old and at high risk for EE, received either a single dose of albendazole, a 14-day course of 20 mg zinc sulfate, or a placebo. Subjects were given the dual-sugar absorption test, and the ratio of lactulose to mannitol (L:M) in urine was used to determine the severity of EE at baseline and 34 days after completion of the assigned regimen. The primary outcome was the change in the L:M.**

RESULTS: **A complete set of urine samples was obtained from 222 of 234 children enrolled and analyzed. The mean baseline L:M was 0.32 ± 0.18 among all children and did not differ among groups (normal L:M range, <0.12). At the end of the study, the L:M ratio had increased more in the placebo group (0.12 ± 0.31) than in the zinc group (0.03 ± 0.20; $P < .03$) or the albendazole group (0.04 ± 0.22; $P < .04$).**

CONCLUSIONS: **Treatment with zinc or albendazole protects against a significant increase in the L:M ratio, a biomarker for EE, in asymptomatic rural Malawian children. These findings could provide insight into the etiology and pathogenesis of EE. Clinicaltrials.gov Number: NCT01440608.**

Keywords: Intestinal Function; Intestinal Integrity; Stunting; Micronutrients; Helminths.

Environmental enteropathy (EE) is a subclinical condition among children in the developing world manifested by T-cell infiltration of the small-bowel mucosa and diffuse villous atrophy.[1–3] EE is reported in 20% to 75% of children younger than 5 years of age from rural sub-Saharan Africa, South America, and South Asia.[4,5] EE is associated with macronutrient and micronutrient malabsorption and stunting.[6,7] Stunting is associated with an increased risk for infection, reduced cognitive development, and a lower capacity for physical labor in adulthood, causing substantial social and economic burdens in affected societies. The etiology of EE is unknown, but poor sanitation and hygiene are implicated by association in its pathogenesis.[8]

Currently, EE is identified in research contexts by the urinary quantification of 2 poorly absorbed, nonmetabolized, orally administrated sugars: lactulose and mannitol.[9] Lactulose, a disaccharide, is passively absorbed across disrupted cell junctions, making it a measure of small-bowel permeability.[3] Mannitol, a monosaccharide, is absorbed across the mucosal surface of the small bowel in addition to passing between permeable cell junctions; it is a measure of the functional surface area of the small bowel.[6]

Because EE is endemic among rural children in the developing world, its pathogenesis is likely to be multifactorial. Chronic parasitic infestations of the small intestine, particularly ascariasis, hookworm, and trichuriasis, are common in rural African children.[10]

Abbreviations used in this paper: EE, environmental enteropathy; L:M, lactulose:mannitol.

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These parasites may be inflammatory stimuli that trigger or perpetuate EE and thus the possibility of treating children with antihelminthic therapy such as albendazole warrants investigation.

Oral zinc therapy reduces childhood mortality from diarrhea by 13%, decreases its incidence by 9%, reduces its prevalence by 19%, and reduces the occurrence of multiple diarrheal episodes by 28%; thus, zinc is recommended by the World Health Organization to be given to every child with an acute episode of diarrhea.[11] Although zinc's mechanism of action has not been elucidated, in vitro evidence suggests zinc directly affects transepithelial ion transport and promotes the maintenance of tight junctions between epithelial cells, whose breakdown otherwise would contribute to chronic immunostimulation and mucosal inflammation.[12]

Given the evidence that zinc and albendazole may address pathogenic factors implicated in EE, a prospective trial of these interventions was undertaken. We studied asymptomatic Malawian children at high risk of EE to test the hypotheses that zinc and/or albendazole would improve their EE, as measured by the dual-sugar absorption test.

Methods

Subjects and Setting

All healthy 1- to 3-year-old children living in Masika, a rural village in southern Malawi, were recruited for the study. Children were eligible if there was no report of more than 3 loose stools per day by the caretaker and if they had no chronic debilitating illnesses such as known human immunodeficiency virus infection, cerebral palsy, or obvious congenital abnormalities. If a child needed acute medical treatment, arrangements were made for a visit with local health staff and the child was not enrolled. If a child showed evidence of severe acute malnutrition (edema suggestive of kwashiorkor or weight-for-height Z-score < -3), the child was excluded from the study and enrolled in a home-based therapeutic feeding program. All children were enrolled during the same week in October 2011.

Most villagers in this area are subsistence farmers, living in mud huts with thatched roofs, and meals are prepared over open wood fires. Local health care is provided by traditional healers or government health surveillance assistants who have completed 2 months of instruction in first aid and disease prevention.

This study was approved by the institutional review boards of both the University of Malawi and Washington University in St. Louis. The study was performed according to Good Clinical Practice guidelines and the Declaration of Helsinki (2000). Chichewa-speaking Malawian research nurses obtained written and oral informed consent from each child's caretaker before enrollment in the study. Caretakers were free to end participation in the study at any time. Community consent for the study also was obtained from the village chief and local health officials. This study was registered with ClinicalTrials.gov with identifier NCT01440608.

Study Design

This study was a randomized, double-blinded, 3-arm, placebo-controlled trial of the efficacy of either oral zinc acetate administered for 14 days or a single dose of albendazole to reduce the risk of EE as assessed by the dual-sugar lactulose:mannitol (L:M) absorption test. The primary outcome was the difference in the urinary L:M ratio before and after the intervention. Secondary outcomes were the amount of lactulose excreted in the urine as a percentage of the amount ingested before and after the intervention, weight gain, and length increase. Urinary L:M, urinary lactulose excretion, and growth parameters were assessed at enrollment and 34 days after the 14-day intervention period, on day 48. Randomization to zinc, albendazole, or placebo was performed prospectively with the use of a coded list compiled from a random number generator with an intended allocation ratio of 1:1:1; the code was fully blinded to the field staff taking measurements, to trial participants and their caretakers, and to the laboratory staff measuring the urinary sugars. A research assistant not involved in the data analysis was responsible for using the random number generator to assign interventions, enroll participants, and assign them to the intervention based on the coded list, which was blinded until all analyses were completed. A sample size of 192 was calculated as necessary to detect a decrease of 0.06 units by the Student t test in the L:M ratio with 95% specificity and 80% power. A decrease of 0.06 units in the L:M ratio is thought to represent the smallest interval change that would be of clinical significance in gut function. The sample size calculations assumed that urinary mannitol and lactulose measurements would be distributed similarly to prior studies, which showed that more than 70% of apparently healthy rural Malawian children had EE, defined as a L:M ratio of 0.12 or higher.

Participation

After obtaining informed consent, demographic information was collected about the child's household, including whether the child's mother and father were alive and what type of water source was available to the household. The Household Food Insecurity Access Scale (version 3) was administered.[13] Anthropometry included an evaluation for edema and measurement of weight and length. Information also was collected regarding the number of days within the past week that the child had diarrhea, visible blood in the stool, abdominal pain, vomiting, cough, and/or a rash. After this initial data collection, each child completed the pre-intervention dual-sugar absorption test.