

**Lactiva and Lysomin: Helping to Save Lives By Improving Oral Rehydration
Solution
Making Innovative Diarrhea Management Accessible**

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Introduction

Every year 2 million children die around the world of complications from diarrhea. It is the number two infectious killer of children under the age of five in developing countries, and one that has captured the attention of leading researches, physicians and international organizations including the World Health Organization and the United Nations.

Even in cases where children's lives are not at risk, the condition is serious – and rampant – particularly in developing countries. According to the World Health Organization there are 4 billion episodes of diarrhea in children each year. Many of these are repeat instances that can create chronic health problems in children, perhaps most significant among them malnutrition, which in turn can weaken children's immune systems and expose them to additional health risks, such as infection, pneumonia and anemia.

The advent in the 1960s of oral rehydration solution (ORS) significantly improved the outlook for children and reduced the number of annual deaths from greater than 5 million to 2 million. However, even with that improvement, diarrhea “is still a major problem. Two million deaths a year is huge,” says William Greenough III, MD, professor of medicine at Johns Hopkins University and a world-renowned expert in pediatric and geriatric diarrhea. “No one should die from diarrhea when we know how to treat it.”

While fewer children are dying around the world from the disease, the problem of the occurrence of the disease has not lessened. Research has shown that breast-fed children have a much lower incidence of diarrhea and other infections than children who do not receive breast milk. Ventria Bioscience's researchers wondered whether adding lactoferrin and lysozyme, two of the key protective proteins found in mother's milk, to oral rehydration solution would lessen the severity or the duration of diarrhea and as such help to improve children's health.

Finding Solutions in Natural Proteins

To test the hypothesis, Ventria and researchers from the University of California at Davis worked with the children's hospital, Instituto Especializado de Salud del Niño, and the world-renowned Instituto de Investigación Nutricional in Lima, Peru, to develop a scientifically verifiable study of the effects of adding Lactiva™ (recombinant human

lactoferrin) and Lysomin™ (recombinant human lysozyme) produced in rice to oral rehydration solution.

Peru was selected as the location for the study in part because diarrhea is a significant problem there. Twenty to twenty-five percent of the 36,000 children who die in the Andean nation every year are victims of diarrhea and the children's hospital in Lima treats hundreds of patients each day who are suffering from diarrhea and its complications.

“Severe diarrhea is one of the problems that most affects countries like ours that have problems of sanitation and extreme poverty,” notes Dr. Juan Rivera, director of gastroenterology at the hospital. “Diarrhea also brings a socioeconomic problem with it: When the child gets sick the parents have to take him to the hospital, and this means an expense – an expense of transport to and from the hospital, in addition to the time the mom or dad has to take off work to be with the child. So in a family that already has economic problems, more problems.”

Dr. Nelly Zavaleta, who helped lead the study, believed the additional of Lactiva and Lysomin to ORS would be a significant improvement. Using rice-based ORS provides the opportunity to give the patient some extra nutrition, she noted, while adding Lactiva and Lysomin help to fight diarrheas caused by gastrointestinal infection. Lactiva also helps the intestinal epithelial cells that have been damaged by diarrhea to recuperate.

“What current oral rehydration solutions don't have is a clear impact on cutting the duration or reducing the severity of acute diarrhea” said Nelly Zavaleta, MD. Ventria's approach to producing the natural protective proteins from breast milk in rice provides a safe, cost-effective way to obtain the previously cost-prohibitive proteins – an innovation that could help save the lives of children around the world.

Outline of the Study

In designing the study, Ventria wanted to compare the effectiveness of three variations in oral rehydration solution: traditional glucose-based oral rehydration solution, the more recently developed rice-based rehydration solution, and rice-based rehydration solution with added lactoferrin and lysozyme. The rice-based rehydration solution was considered a particularly good vehicle for Ventria's Lactiva™ and Lysomin™ because the two proteins are grown in rice (which is then processed to extract the relevant protein).

“The idea would be that you could combine something that's safe and encourages the return of the intestinal tract to normal, along with oral rehydration. This would be what we all would hope for,” noted Greenough.

The randomized, double-blind study enrolled 140 boys aged 5 to 33 months who were suffering from acute diarrhea for less than 72 hours and who had not been treated with

antibiotics. Children who were exclusively breastfed or who were suffering severe malnutrition were excluded from the study.

The children in the study were divided into three groups and randomly given one of the three types of oral rehydration solution. During the first 48 hours they were monitored in the children's hospital's Oral Rehydration Unit by a nurse and a pediatrician. Then they were sent home and were visited every day from Days 3-6 by a health worker from the Nutrition Institute who was trained in the parameters of the study and could also counsel parents about proper methods for managing diarrhea. The children returned to the clinic for evaluation on Days 7 and 14.

In all cases the children's intake and output were monitored closely until the diarrhea stopped, a maximum of 14 days was reached, or the children withdrew from the study, as happened in one case for reasons unrelated to the research. A total of 135 children completed the study.

Clinically and Statistically Significant Results

The study showed that children who took the rice-based oral rehydration solutions with added Lactiva and Lysomin were sick for less time. Children in the Lactiva/Lysomin ORS group were sick for 3.67 days on average, as compared to 5.21 days for children in the other groups.

Reduction in the severity of the illness, as defined by the percentage of children with solid stool for 48 hours was significantly higher in the Lactiva/Lysomin ORS group – with 85.1 percent of children reaching this landmark – while just 69.2 percent of the control ORS children reached the 48-hour milestone.

In addition, the percentage of children who relapsed after 48 hours without diarrhea was lower in the Lactiva/Lysomin ORS group than in the control group (8.5 percent compared to 18.7 percent); these results, while not statistically significant, were considered clinically important.

The study's results are described in a presentation at the Pediatric Academic Societies 2006 annual meeting. The research, including the notion of making the proteins affordable by producing them in rice, has caught the attention of researchers and physicians around the world.

“This innovation makes something accessible to everyone, a win-win combination,” Greenough said. “We know that babies that drink breast milk do not get diarrhea with anywhere near the same frequency as children who are not breast fed, so if you can take the important components of breast milk and extend them to children who are not breastfeeding and older people this would be a huge advantage. The initial study in Peru suggests that (Ventria's proteins) have some substantial advantages that would address what is still a very serious problem and put a solution within reach of people that do not have resources. The breakthrough has been the ability to make these human proteins in

rice. This takes something that costs thousands of dollars for a gram down to something that is relatively inexpensive and could be used with an inexpensive medical food like oral rehydration solution.”

Looking to the future

Now that the study has yielded positive results, Ventria is looking both at further research into Lactiva and Lysomin’s benefits for children, as well as for older people and travelers. Greenough is looking forward to the possibilities as well:

“I am hoping that (Lactiva and Lysomin) might be the first thing that would be widely added to oral hydration, which is consumed by at least half of the world’s children,” he said. “This is what we call the Holy Grail. We’d like to have something that both hydrated people and could shorten the illness. That is what every mother would want for their child.”