

Evaluation of safety and efficacy of a novel anti-secretory anti-diarrheal agent Crofelemer (NP-303), in combination with a single oral dose of azithromycin for the treatment of acute dehydrating diarrhea caused by *Vibrio cholera*

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The effects of crofelemer were evaluated in patients with acute dehydrating watery diarrhea and confirmed *Vibrio cholerae* infection. Patients were randomized to oral doses of placebo or crofelemer at doses of either 125 mg or 250 mg every 6 hours for 2 days. A total of 100 adult patients between the ages of 18 and 55 with acute, severely dehydrating watery diarrhea from cholera were enrolled in this study. After a four hour period of rapid rehydration therapy patients were randomized 1:2:2 to placebo or 125 mg or 250 mg oral dose of crofelemer. Enrollment was based on the assessment of rehydration therapy, a confirmed diagnosis of *Vibrio cholerae* and a high watery stool purging rate of >10 mL/kg. Crofelemer or placebo doses were initiated about one hour after the single oral dose of azithromycin (1 gm). The primary objective was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours on the background of azithromycin and rehydration therapy. The duration of diarrhea was monitored and assessed as the time from randomization to resolution of diarrhea. Crofelemer was well tolerated and there were no drug related adverse events in this study. The acute reduction of the dehydrating watery diarrhea, measured as stool volume output normalized by body weight, was evaluated in the first 6- and 12-hour intervals, since it has been previously reported that the reduction of watery stool output is similar during the initial period of 12-18 hours, with or without the use of antibiotics. Both doses of crofelemer produced approximately a 25-30% reduction in median watery stool volumes in the 0-6 and 0-12 hour period following initiation of therapy. Oral doses of crofelemer showed a strong trend towards reduction of watery stool output in the 0-6 hour and 0-12 hour intervals (p=0.07). Furthermore, three patients were determined to be outliers based on stool volume output or duration of diarrhea. Upon exclusion of the three outlier patients, the crofelemer dose of 125 mg produced a significant reduction in the normalized stool output (p=0.028) and the dose of 250 mg crofelemer showed a strong trend for reduction of watery stool output (p=0.07). These results show that crofelemer produced rapid and clinically meaningful improvement in the treatment of acute dehydrating watery diarrhea in combination with azithromycin and rehydration therapy. Further studies are needed to fully evaluate the dose-response of crofelemer in treating severely dehydrating watery diarrhea in cholera patients.

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